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Avoidance in Fear Conditioning and Anxiety Disorders

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Avoidance in Fear Conditioning and Anxiety Disorders

A dissertation submitted in partial satisfaction of the requirements for the degree of Doctor of Philosophy in Psychology

by

Bita Mesri

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ABSTRACT OF THE DISSERTATION

Avoidance in Fear Conditioning and Anxiety Disorders

by

Bita Mesri

Doctor of Philosophy in Psychology

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Professor Michelle G. Craske, Chair

This dissertation is a three-paper investigation of ways to improve treatment outcomes for anxiety disorders.

Study 1 investigates whether training implicit approach or avoidance to feared stimuli augments or impedes fear extinction. We also investigate whether baseline explicit avoidance predicts extinction performance or future avoidance behavior. Extinction performance is used as a proxy for exposure therapy. Results revealed no effect of training implicit approach or avoidance on extinction performance nor future behavioral avoidance. Baseline explicit avoidance did not predict extinction performance, whereas it did predict future behavioral avoidance. Findings suggest that explicit avoidance may not affect fear extinction in an unambiguous fear-conditioning paradigm, but that it may affect future tendency to approach feared stimuli.

Study 2 investigates behavioral avoidance as a moderator of treatment outcome for two behavioral therapies for social anxiety disorder. Individuals who were highly behaviorally avoidant on a public speaking task had better long-term treatment outcomes following cognitive behavioral therapy (CBT) than acceptance and commitment therapy. From a deficit correction model, individuals who are more behaviorally avoidant may benefit from a treatment that more systematically targets that avoidance. A version of this work has been published in the *Journal of Behavior Therapy and Experimental Psychiatry* (2017).

Study 3 investigates interoceptive and in vivo avoidance as moderators of treatment outcome for two different CBTs for panic disorder. Individuals who displayed more in vivo avoidance at baseline had better outcome following CBT with interoceptive exposures than CBT with interoceptive and in vivo exposures. This suggests that avoidant individuals benefit more from a therapy that targets their primary interoceptive concerns as opposed to one that expands to in vivo avoidance.

Taken together, these studies aim to improve treatment outcomes in behavioral therapies for anxiety disorders. Study 1 suggests that retraining implicit approach avoidance behavior does not augment fear extinction in an unambiguous fear conditioning design. Studies 2 and 3 suggest that individuals with anxiety disorders who are highly avoidant at baseline may benefit from treatments that explicitly target their primary avoidance. This line of research can provide evidence-based methods for treatment selection to better match individuals to specific therapies. Additionally, all three studies contribute to our understanding of implicit and explicit avoidance in fear and anxiety.

The dissertation of Bita Mesri is approved.

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DISSERTATION INTRODUCTION

Anxiety disorders are the most prevalent psychological disorders, affecting approximately one third of adult Americans (Kessler et al., 2005; Kessler, Petukhova, Sampson, Zaslavsky, & Wittchen, 2012). These disorders are associated with significant distress and functional impairment (Olatunji, Cisler, & Tolin, 2007). Left untreated, anxiety disorders can lead to the development of other psychological disorders including mood and substance use disorders (Brown, Campbell, Lehman, Grisham, & Mancill, 2001; Zahradnik & Stewart, 2009). Exposure-based treatments such as cognitive behavioral therapy (CBT) are among the most empirically supported treatments for anxiety (Barlow, 2002; Norton & Price, 2007). Yet, response rates to CBT are approximately 50%, making improvements for treatment response necessary (Loerinc et al., 2015).

Susceptibility to fear conditioning and deficits in extinction are believed to contribute to the onset and maintenance, respectively, of excessive and impairing anxiety (Barlow, 2002; Lerman, 2003). In aversive classical conditioning, fear is acquired when a neutral conditional stimulus (CS) is repeatedly paired with an innately aversive unconditional stimulus (US). As a result of this repeated pairing, the CS comes to predict the US, eliciting a conditional fear response (CR). Fear is extinguished by presenting the CS numerous times in the absence of the US.

In 1913, Bechterev conducted the first experiment documenting an avoidance response to aversive stimuli. He followed a neutral CS with an electric shock (US) to dogs' paws. When the CS was later presented, the dogs moved their paws to avoid the shock. Classical conditioning explains the learned fear of a CS, but fails to explain this learned avoidance behavior. In classical

conditioning, participants' behaviors do not affect whether or not they receive the US, whereas in this learned avoidance behavior, moving their paws affects whether they receive the shock (Herrnstein, 1969).

Soon, experiments were conducted that included both classical conditioning and an explicit avoidance procedure (Brogden, Lipman, & Culler, 1938; Solomon, Kamin, & Wynne, 1953). Solomon, Kamin, and Wynne (1953) placed dogs in chambers that were divided by a short barrier into two compartments. A light (CS) signaled the administration of electric shocks (US) in one compartment of the chamber. After a few trials, the dogs learned that the light predicted the shock and would jump over the barrier to avoid the shock. Instrumental conditioning was used to explain this avoidance response. In instrumental conditioning, individuals are motivated to engage in certain behaviors through reward and punishment. In this case, avoidance behavior was thought to be negatively reinforced by the removal of the aversive stimulus. However, instrumental learning could not be used to explain how the absence of something was reinforcing.

Mowrer's two-factor theory of fear and avoidance (1947) attempted to explain avoidance behavior by combining fear conditioning and operant conditioning. The first factor of Mowrer's theory was that fear of a neutral stimulus can be learned through classical conditioning. Through repeated pairing with a US, a neutral stimulus (CS) evokes fear. The second factor was that avoidance of a CS is learned through operant conditioning. The avoidance behavior (e.g., moving paw, jumping barrier) is learned through negative reinforcement because the avoidance behavior ends the feared CS. This component filled the previous gap because Mowrer explained avoidance behavior in terms of escape from a CS rather than in terms of prevention of US. This theory was seminal in the creation of exposure-based treatments for anxiety. Nevertheless, the

theory fails to explain some other features of avoidance learning (Herrnstein, 1969). First, avoidant responding can be learned even if the response does not terminate the CS or reduce the duration of CS, so long as the response prevents the US (Bolles, Stokes, & Younger, 1966; Soltysik, Wolfe, Nicholas, Wilson, & Garcia-Sanchez, 1983). Second, avoidance behaviors can be taught without a CS if the avoidance behavior simply reduces the frequency of the US (Herrnstein & Hineline, 1966). Third, if a CS can be followed by an avoidance response, individuals report less fear of the CS (Lovibond, Saunders, Weidemann, & Mitchell, 2008; Mineka, 1979; Solomon, Kamin, & Wynne, 1953). This is problematic because Mowrer's theory hinges on the CS being a feared stimulus.

The safety signal theory of avoidance was created in response to the shortcomings of Mowrer's theory (Gray, 1975; Hammond, 1967). In Mowrer's two-factor theory, avoidance behavior was motivated by negative reinforcement through the removal of a feared CS. In the safety signal theory, avoidance is motivated by positive reinforcement through the addition of positive feedback related to feeling safe (Rachman, 1984). This explains why avoidance responses can be learned even if they do not affect the duration or the occurrence of the CS. It also explains why people's fears of the CS are reduced when they learn an avoidance behavior.

The safety signal theory of avoidance also helps explain why avoidance impedes fear extinction. In the previously explained experiment by Solomon, Kamin, and Wynne (1953) in which dogs jumped over barriers to avoid shocks, one of the dogs engaged in the avoidance behavior on 650 successive trials after only receiving a few shocks. The persistence of this avoidance response was found even after the experimenter had unplugged the shock device. Dogs continue to engage in the avoidance behavior because they are motivated to receive the safety feedback. By continuously performing the avoidance response, they associate any safety

to the avoidance response rather than the situation. This prevents the participant from learning that the cage is no longer wired to provide shocks.

An alternative explanation to avoidance impeding extinction can be derived from the Rescorla-Wagner (1972) model. This model theorizes that learning increases as the discrepancy between what is expected to occur and what actually occurs increases. No learning occurs when what is expected matches what occurs. In a fear-conditioning model in which the presence of a tone (CS) precedes an unexpected shock (US), animals have the greatest fear learning after the first few shocks. As the tone is continuously paired with the shock, the animals continue to associate the tone with fear, but at a slower pace of learning. With enough pairing, the animals expect the shock to follow the tone and no new learning occurs across subsequent trials. Fear extinction occurs when the tone, which is expected to cue the shock, is no longer paired with the shock. Through the discrepancy between expecting a shock and not receiving a shock, the animals learn that the tone is no longer predictive of shock and fear extinguishes.
During the extinction phase, if the avoidance behavior is performed, there is no discrepancy between what is expected and what actually occurs, so there is no learning. Because the animal continues with the old learning that the CS is predictive of the US, the animal will continue to fear the CS even if it is no longer actually paired with the US.

Seligman and Johnston's "cognitive theory of avoidance learning" (1973) also relies on the idea that learning occurs during expectancy violations. Their theory highlights that cognitions related to expectations mediate this learning. Humans or animals learn to expect an aversive stimulus if an avoidance response is not performed and they learn not to expect the aversive stimulus if an avoidance response is performed. This theory expands on previous ones by

explaining how individuals can acquire a fear of CS after simply being informed that a specific CS predicts a US (informational transmission; Kirsch, Lynn, Vigorito, & Miller, 2004).

Lovibond's (2006) expectancy model expands on Seligman and Johnston's cognitive theory by theorizing that fear acquisition includes both implicit (i.e., unconscious, reflexive) and explicit (i.e., conscious) components. In this model, during fear acquisition, the CS elicits fear through both implicit (e.g., Pavlovian) learning and explicit (e.g., cognitive) expectation that the CS predicts the US. During extinction learning, individuals use their explicit outcome expectations to decide whether to respond in avoidance or not. In Lovibond's theory, anxiety affects the expectancy of the aversive outcome, which in turn affects avoidance behavior. Avoidance behavior then impedes extinction by preventing individuals from learning that the CS no longer predicts the US (Lovibond, Mitchell, Minard, Brady, & Menzies, 2009).

Cognitive models of anxiety posit that individuals with anxiety think differently from healthy controls. Compared to non-anxious individuals, anxious individuals demonstrate irrational or excessive threat appraisals, which result in exaggerated beliefs about the probability and distress of an aversive outcome (Butler & Mathews, 1987; Rachman, 1994). By being exposed to situations that they previously avoided, individuals are able to learn that they often over-predict the probability and distress of an aversive outcome. However, mere exposure to a feared situation may not be enough to disconfirm false beliefs if individuals use covert methods of avoidance such as "response aids" or "within situations safety behaviors" (Bandura, Jeffery, & Wright, 1974; Salkovskis, 1991).

Safety behaviors are subtle behaviors or even thoughts used to avert a feared outcome (Salkovskis, 1991). The use of safety behaviors explain why an individual with panic disorder who has had over 30 panic attacks that did not end in fainting still fears fainting. If the individual

is engaging in a safety behavior such as taking an anxiolytic or sitting down, the individual learns that the safety behavior prevented fainting instead of learning that panic attacks do not cause fainting. The individual attributes safety to the safety behavior rather than the feared situation. Just like overt avoidance, which was previously discussed in the "safety signal theory of avoidance," covert avoidance in the form of safety behaviors prevents exposure learning or fear extinction (Salkovskis, 1991). Despite the overwhelming literature supporting dropping safety behaviors during exposure therapy, there are a few studies that find comparable outcomes between exposures with and without safety behaviors (Milosevic & Radomsky, 2008; Piccirillo, et al., 2016; Rachman, Craske, Tallman, & Solyom, 1986). This has prompted some to suggest that the judicious use of safety behaviors at the beginning of exposure therapy or in situations of extreme fear may be harmless (Rachman, Radomsky, & Shafran, 2008). In these studies, safety behaviors were used sparingly. Conceivably, the overall benefit of exposure therapy may have overshadowed the early use of safety behaviors.

Overt and covert avoidance are key features across many anxiety disorders making them potential transdiagnostic maintenance factors (Barlow, 2002).

Panic disorder

Individuals with panic disorder are overly concerned about the consequences of having a panic attack (American Psychiatric Association, 2013). They may worry that a panic attack will lead to fainting, having a heart attack, dying, or going crazy (American Psychiatric Association, 2013). In the previous panic disorder example, individuals may avoid situations that may increase their heart rate such as going to the gym or taking a hot shower. They may fear that an increase in heart rate may induce a panic attack and lead to fainting. Safety signals may include taking an anxiolytic or sitting down when noticing an increased heart rate (Helbig-Lang et al.,

2014). These avoidance strategies are problematic in that they block the ability to learn that a panic attack does not actually lead to fainting or death (Salkovskis, Clark, & Gelder, 1996). Additionally, avoidance of many different situations can affect the quality of life of an individual who may no longer be able to engage in everyday activities such as exercise. Indirect evidence for the maintenance roles of safety behaviors and avoidance of panic disorder is found through short and long-term reductions in panic anxiety following exposure treatments that encourage giving up safety behaviors (Clark et al., 1994).

Agoraphobia

Individuals with agoraphobia have a fear of being in a situation where they may not be able to escape if they have a panic attack (American Psychiatric Association, 2013). Commonly avoided situations include shopping malls, subway stations, or concerts (American Psychiatric Association, 2013). In severe cases, individuals may be unable to leave their home.
Safety behaviors may include locating all exits before entering a room, staying near an exit, or only entering situations if a friend is present to ensure safety (Rachman, 1984). Exposure therapy accompanied with dropping safety behaviors and belief disconfirmation strategies have been found to be more effective than habituation-based exposure therapies for agoraphobia (Salkovskis et al., 2007). Even a single exposure with instructions to drop safety behaviors led to significant improvements in agoraphobic symptoms compared to exposures without instructions to drop safety behaviors (Salkovskis, Clark, Hackmann, Wells, & Gelder, 1999).

Social Anxiety Disorder

Individuals with social anxiety disorder fear being negatively judged, rejected, or humiliated (American Psychiatric Association, 2013). Overt avoidance may take the form of completely avoiding social situations (e.g., parties, meetings). Individuals with social anxiety

may select socially isolating jobs (e.g., truck driver) and may avoid in-person interactions as much as possible (e.g., get groceries delivered to their house). When forced to have a social interaction, they may use safety behaviors such as avoiding eye contact or responding with short answers, believing that these behaviors may lessen their chances of being rejected (Wells et al., 1995). Paradoxically, these safety behaviors, which are meant to decrease rejection, may actually increase rejection (Alden & Bieling, 1998). For example, the person who avoids eye contact may be seen as aloof or cold. In addition to explicit avoidance, individuals with social anxiety disorder demonstrate implicit avoidance tendencies toward crowds with angry faces (Lange, Keijsers, Becker, & Rinck, 2008). There is overwhelming evidence that exposure therapy and CBT with specific instructions to drop safety behaviors have better long-term outcomes than treatments that do not instruct individuals to drop safety behaviors (for a review, see Piccirillo, Dryman, & Heimberg, 2016).

Specific Phobia

Individuals with specific phobias have intense persistent fears of one specific situation, animal, or object (American Psychiatric Association, 2013). Often, specific phobias fall into one of the following categories: animals (e.g., spiders, dogs), natural environments (e.g., heights), blood/ injury/ injections (e.g., getting a shot), or situations (e.g., airplane, elevators) (American Psychiatric Association, 2013). An example of overt avoidance is an individual with a specific phobia of heights who avoids hiking. An example of a safety behavior may be going hiking, but staying extremely far from the edge, believing that getting too close will lead to death. In addition to explicit avoidance, individuals with a specific phobia of spiders were found to demonstrate implicit avoidance tendencies to images of spiders (Rinck & Becker, 2007). Individuals with claustrophobia who were randomized to exposures with explicit instructions to

focus/ reappraise threat or drop safety behaviors, fared better than individuals who were given the option of using safety strategies (Sloan & Telch, 2002). In a follow-up study, Powers, Smits, and Telch (2004) randomized individuals with claustrophobia to one of five groups: 1. Exposure only, 2. Exposure with safety behavior availability, 3. Exposure with safety behavior utilization, 4. Credible placebo treatment, and 5. Waitlist. Response rates were 94%, 45%, 44%, 25%, and 0% respectively, pointing to the superiority of exposures without safety behaviors. Likewise, in height and driving phobics, Williams, Dooseman, and Kleifield (1984) found that exposure therapy combined with fading safety behaviors was more effective than exposure alone.

Generalized Anxiety Disorder (GAD)

Individuals with GAD spend most of their day worrying about many different topics such as finances, family, health, or work (American Psychiatric Association, 2013). GAD is the only anxiety disorder that is not categorized by behavioral avoidance in the DSM-5 (American Psychiatric Association, 2013). This may be because fears in GAD are often future-oriented or not tangible (e.g., fearing that your child will die), making it difficult to identify behavioral avoidance. Additionally, fear and avoidance are more heterogeneous in a sample of GAD as opposed to one of claustrophobia. For example, an individual with GAD who is worried about future finances may avoid opening bills, whereas one who is worried about future health may avoid going to the doctor. General avoidance behaviors that have been found across individuals with GAD include checking as a form of reassurance seeking, making lists, and avoiding making decisions (Beesdo-Baum et al., 2012). It is theorized that the act of worrying itself is a form of cognitive avoidance aimed at reducing emotionality triggered by a previous thought (Borkovec, Alcaine, & Behar, 2004; Schut, Castonguay, & Borkovec, 2001). There is some evidence that behavioral avoidance somewhat decreases after treatment for GAD (Beesdo-Baum et al., 2012).

Additionally, there is evidence that high degrees of behavioral avoidance and safety behaviors following treatment predict poor long-term treatment outcomes (Beesdo-Baum et al., 2012). More research on behavioral avoidance and safety behaviors in GAD is necessary (Mahoney et al., 2016).

Post Traumatic Stress Disorder (PTSD)

PTSD is a disorder that develops after an individual has experienced a traumatic incident such as sexual assault or warfare (American Psychiatric Association, 2013). It is no longer part of the DSM-5 Anxiety Disorders, but it is considered an affective disorder marked with high negative affect (DiMauro, Renshaw, & Kashdan, 2016; Ehlers & Clark, 2000). Symptoms of PTSD include mental avoidance or behavioral avoidance of places, situations, or cues that remind the individual of the traumatic incident (American Psychiatric Association, 2013). This avoidance is thought to, at least partially, maintain the disorder (Bryant & Harvey, 1995; Dunmore, Clark, & Ehlers, 2001; Feeny & Foa, 2006). Moreover, in addition to explicit avoidance, individuals with PTSD have been found to have greater implicit avoidance of high threat images compared to healthy controls (Fleurkens, Rinck, & van Minnen, 2014). Indirect evidence for the role of avoidance in maintaining PTSD is evident from the positive response to prolonged exposure treatment (Cusack et al., 2016; Nacasch et al., 2011; Steenkamp, Litz, Hoge, & Marmar, 2015).

Conclusion

Overt and covert avoidance are important transdiagnostic factors in the onset and maintenance of anxiety disorders. Across a set of three studies, we aim to use our understanding of avoidance to improve treatment outcomes for anxiety disorder. Study 1 investigates whether retraining implicit approach/ avoidance tendencies toward feared images enhances or hinders the

process of fear extinction. Uncovering methods that improves fear extinction can then potentially be used to augment exposure therapy, an essential treatment for anxiety disorders. Studies 2 and 3 investigate whether individuals with high baseline avoidance fare better in one of two treatments for anxiety disorders. Better matching individuals to treatments has the potential to enhance treatment effectiveness.

Study 1

Baseline Characteristics as Predictors of Fear Acquisition, Extinction, and a Behavioral Forced Choice Test

Abstract

Background and Objectives: Susceptibility to fear conditioning and deficits in extinction are believed to contribute to the onset and maintenance, respectively, of excessive and impairing anxiety. Avoidance of fear stimuli is thought to impede fear extinction. This study aims to investigate whether training implicit approach or avoidance to fear stimuli affects fear extinction and overt avoidance behavior. Additionally, we aim to increase our wealth of knowledge of baseline characteristics that predict fear acquisition, extinction, and overt avoidance behavior.

Methods: Participants (N = 135) were assessed at baseline for explicit avoidance, state anxiety, and trait anxiety. They underwent differential fear conditioning during which they acquired fear of one stimulus (CS+) and not of another stimulus (CS-). Participants were then randomized to one of four groups, wherein they received implicit approach training to the CS+, avoidance training to the CS+, 50-50 training, or no training. This was followed by fear extinction during which neither stimulus was paired with an aversive unconditional stimulus. A behavioral forced-choice test was used to measure overt behavioral avoidance of fear stimuli.

Results: There was no significant effect of group assignment on extinction performance or overt avoidance behavior. State anxiety and explicit avoidance predicted overt approach behavior to fear stimuli. Baseline state anxiety predicted US expectancy during fear acquisition, whereas trait anxiety predicted US expectancy during fear extinction.

Limitations: One main limitation is that all experimental procedures were conducted on the same day. Considering state anxiety predicted acquisition response whereas trait anxiety predicted extinction response, future studies may benefit from a more comprehensive measure of anxiety.

Conclusions: Findings inform baseline characteristics that predict fear acquisition, extinction, and overt avoidance behavior.

Introduction

Anxiety disorders have the highest lifetime prevalence of all psychological disorders; they affect 33.7% of adult Americans (Kessler, Petukhova, Sampson, Zaslavsky, & Wittchen, 2012). These disorders are associated with significant distress or impairment. Susceptibility to fear conditioning and deficits in extinction are believed to contribute to the onset and maintenance, respectively, of excessive and impairing anxiety (Barlow, 2002). Uncovering methods that augment extinction may improve exposure therapy, which is currently used to treat anxiety disorders.

In Pavlovian aversive conditioning, fear is acquired when a neutral conditional stimulus (CS) is repeatedly paired with an innately aversive unconditional stimulus (US). As a result of this repeated pairing, the CS comes to predict the US, eliciting a conditional fear response. Fear is extinguished by presenting the CS numerous times in the absence of the US. In differential conditioning, one CS is always paired with the US (i.e., CS+) and another CS is never paired with the US (i.e., CS-). The Rescorla-Wagner model of fear learning (1972) theorizes that extinction learning relies on the discrepancy between what is expected and what actually happens (i.e., error correction). The Pearce-Hall model (1980) emphasizes CS salience (i.e., how noticeable the CS is) for extinction learning. Developing techniques that enhance extinction learning by enhancing the salience of the CS (thereby possibly enhancing error correction) can inform remediation of damaging levels of anxiety.

Explicit avoidance has been shown to impede extinction by preventing individuals from learning that the CS no longer predicts the US (Lovibond, Mitchell, Minard, Brady, & Menzies, 2009). Yet, anxiety, fear, and fear conditioning are generally thought to involve implicit (i.e., reflexive, non effortful) reactions as well as explicit (i.e., conscious) processes (LeDoux, 1996).

In order to gain a full understanding of the effects of avoidance on extinction, there is a need to evaluate the effect of implicit as well as explicit avoidance processes. Recently, training tools to modify implicit approach avoidance tendencies to fear stimuli have been helpful in populations of social anxiety disorder and alcohol addiction (Taylor & Amir, 2012; Wiers, Eberly, Rinck, Becker, & Lindenmeyer, 2011). To date, there has only been one study assessing whether training implicit approach or avoidance to fear stimuli augments extinction learning within a fear-conditioning paradigm. Conceivably, implicit approach training to the CS+ would augment extinction performance by enhancing the salience of the CS+. A previous study failed to uncover an effect of implicit approach avoidance training on subjective and physiological fear performance during extinction (Krypotos, Arnaudova, Effting, Kindt, & Beckers, 2015). This study sought to re-investigate this by modifying the procedure and methodology. This study also expands on the previous one by including a behavioral forced-choice task following extinction to measure overt avoidance behavior. Whereas training implicit approach or avoidance may not affect extinction performance, it may affect future behavioral avoidance.

In addition to experimentally manipulating implicit approach avoidance tendencies, we were interested in the effects of baseline explicit avoidance on fear acquisition, extinction, and overt avoidance behavior. It has been suggested that some individuals have temperamental vulnerabilities that make them more likely to acquire fear and less likely to extinguish it (Mineka & Zinbarg, 2006; Orr et al., 2000). More specifically, individuals with anxiety seem to have heightened fear responses to both the CS+ and CS- suggesting that they have difficulty inhibiting fear even to neutral stimuli (Davis, Falls, & Gewirtz, 2000; Duits et al., 2015; Gazendam, Kamphuis, & Kindt, 2013; Lissek et al., 2005). However, aside from comparing anxious to non-anxious populations, there has been little exploration of which baseline characteristics affect fear

extinction and avoidance behavior (Lissek et al., 2005). Examining baseline characteristics in non-anxious samples may allow us to identify characteristics that make individuals more susceptible to fear conditioning or the development of anxiety disorders without confounding present symptoms of anxiety. To our knowledge, only one study has looked at non-anxiety baseline characteristics in a differential fear-conditioning paradigm (Otto et al., 2007). They found that high behavioral avoidance was associated with decreased fear response during fear acquisition. Moreover, there is evidence that high avoidance interferes with extinction learning (Lovibond, Davis, & O'Flaherty, 2000; Lovibond, Mitchell, Minard, Brady, & Menzies, 2009). Together, this would suggest that avoidance interferes with overall learning. This study sought to expand upon previous findings by using a measure of explicit avoidance that asks individuals to rate their avoidance of "uncomfortable" situations as opposed to a standard list of possible phobic situations (e.g., hospital, concert) (Marks & Mathews, 1979). Additionally, we expand on the previous study by including a behavioral measure of in vivo avoidance following extinction.

This study assessed whether training approach or avoidance augments or impedes extinction performance and whether it affects future approach avoidance behavior. We expected that implicit training to approach rather than avoid the CS+ would attenuate fear response by enhancing its salience. Additionally, we investigated baseline explicit avoidance as a predictor of fear acquisition, fear extinction, and an in vivo approach avoidance task. We hypothesized that individuals with higher behavioral avoidance of uncomfortable situations would exhibit deficits in fear acquisition and extinction compared to individuals with lower avoidance. We also hypothesized that they would be more likely to avoid fear stimuli on a behavioral test. Secondary analyses investigated baseline state and trait anxiety as predictors of fear acquisition, extinction, and an in vivo approach avoidance task. We hypothesized that individuals who reported greater

state and trait anxiety would exhibit larger fear response during acquisition, deficits in fear extinction, and greater likelihood to avoid fear stimuli on a behavioral test. This experiment could make an important contribution to the literature on extinction learning in humans.

Method

Participants

Participants (N = 135) were recruited from undergraduate psychology courses at the University of California, Los Angeles. Participants were given course credit for their participation. Exclusionary criteria include 1) being less than 18 years old, 2) not understanding English, 3) having any heart condition, and 4) being told by a physician to stay out of stressful environments. The sample was predominantly female (80%), young (M age = 20.22), as well as racially and ethnically diverse. Participants described themselves as Asian (33%), White (23%), Multiracial (6%), Black/ African American (4%), American Indian/ Alaska Native (1%), Native Hawaiian/ Other Pacific Islander (1%), other (25%), and declined to answer (7%). 28% identified as Hispanic/ Latino.

Materials

Self-report questionnaires. At baseline, participants completed the Acceptance, Safety Behaviours, Escape, and Avoidance Scale (AcSEAS; McEvoy, LeBeau, Page, & Craske, in prep). The AcSEAS is a 17-item questionnaire with three subscales. The avoidance subscale, which is comprised of 5 items, was used. Sample items include "I avoid uncomfortable situations at all costs" and "If I am concerned about an upcoming situation, then I just won't go." Participants were asked to rate how typical or characteristic each item is on a 5-point Likert scale from 1 (*not typical at all*) to 5 (*very typical)*. The avoidance subscale of the AcSEAS has good internal consistency (Cronbach's α = .87, average inter-item correlation = .58) and test-retest

reliability ($r = .61, p < .001$). In our sample, $M = 17.36$, $SD = 4.58$, Cronbach's $\alpha = .80$. A factor analysis revealed an eigenvalue of 2.30 for the first factor and 0.09 for the second factor. Only the first factor had an eigenvalue greater than 1, suggesting that the scale items are unidimensional; therefore, we retained only one factor. The factor model explained 23.95% of the variance in item 1, 55.13% in item 2, 63.54% in item 3, 43.89% in item 4, and 43.41% in item 5.

At baseline, participants also completed The State-Trait Anxiety Inventory (STAI), a 20-item measure of state and trait anxiety (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983). Example items include "I feel nervous" and "I feel tense." Each item is rated on a 4-point Likert scale from 1 (*not at all)* to 4 (*to a great extent)*. The STAI demonstrates good internal consistency (State $\alpha = .83$ - $.92$, Trait $\alpha = 0.90$) and the STAI-Trait has good test-retest reliability ($r = .73$ - $.86$) (Spielberger et al., 1983). In our sample, STAI-State $M = 34.64$, $SD = 8.68$ and STAI-Trait $M = 40.12$, $SD = 9.72$.

Apparatus and Stimuli. Two geometric shapes of different colors (blue disk, green cube) were the CSs, counterbalanced as CS+ or CS- across participants. The CSs appeared one at a time in the center of the screen for 8 s. The CS+ was paired with the US during acquisition training. The CS- was never paired with the US. The US was a 1 s scream sound presented through headphones at 82 db that coterminated with the CS+. Scream sounds have been previously and successfully used as USs (Hamm, Vaitl, & Lang, 1989; Joos, Vansteenwegen, & Hermans, 2012; Lau et al., 2008; Neumann & Waters, 2006; Sperl, Panitz, Hermann, & Mueller, 2016). E-prime software was used for stimulus delivery (Psychology Software Tools, Inc., Pittsburgh, PA, USA).

Implicit Approach/ Avoidance Training Task. Our training task was based on

procedures used by Krypotos et al. (2015) wherein participants were asked to respond differentially to background stimuli of the CS+ or CS-. We made some modifications to the Krypotos et al. (2015) procedures. First, instead of approaching or avoiding images on a computer screen by using a joystick, participants pressed "c" and "n" keys on a keyboard based on the orientation (vertical or horizontal) of the background stimuli. Pressing the "c" and "n" keys would cause the CS images to increase or decrease in size giving the illusion that the image was getting closer or further away from the participant. Second, instead of responding to the tilt of a white background, participants responded to the orientation (horizontal or vertical) of a white background. This changed was made with the intent of increasing the salience of the background. Third, we increased the training to 3 blocks of 300 trials (250ms ITIs) with 4 practice trials before each block. Practice trials included images that were different from the CSs. Similar to the Krypotos et al. (2015), if participants pressed the wrong key in reaction to a background, a red X appeared on the screen and they were required to re-do the trial until they pressed the correct key. This was done in order to ensure that images became larger or smaller according to group assignment instead of incorrect responses.

US expectancy. During acquisition and extinction, participants were asked to rate their expectancy of the US using a dial from "certain no noise" to "certain noise." The midpoint of the dial was labeled "uncertain." The following values were added for analyses and graphs -20 (certain no noise), 0 (uncertain), and 20 (certain noise). Participants were told they could move the dial up and down any point on this range. They were told to use the dial continuously throughout the experiment even if the CS was not on the screen. The words "scream sound?" appeared on the screen 1 s after CS onset and 1 s before US onset as a reminder to continuously use the dial. Mean US expectancy ratings were calculated from 1 s to 7 s after CS onset.

Skin Conductance Response. Skin conductance response (SCR) was measured using Biopac MP150 and Acqknowledge 4.0 programs (Biopac Systems, Inc., Goleta, CA, USA). One disposable electrode was placed on the distal phalanx of the middle finger and one on the distal phalanx of the index fingers of the non-dominant hand. SCR was calculated as the difference between the maximum skin conductance level (measured in microsiemens) during 6 s following CS onset and the mean skin conductance level during 2 s prior to CS onset. Data were range corrected by dividing each SCR by that individual's maximum skin conductance level to the US. The maximum skin conductance level to the US was calculated as the difference between the maximum skin conductance level during 6 s following US onset and the mean skin conductance level during 2 s prior to CS onset. The square root of these range-corrected skin conductance levels was used to normalize the distribution prior to statistical analyses. SCRs were scored as zero if there was no observable peak in skin conductance level within 1 to 6 s following CS onset.

Behavioral Forced Choice Test. Participants were presented with two boxes (12.7 cm x 10.16 cm). One box included 5.08 cm x 2.54 cm chocolates wrapped in the image of the CS+. The other box included the same sized chocolates wrapped in the image of the CS-. The hand in which the research assistant held each box was randomized so that the CS+ and CS- were held in each hand 50% of the time. Participants were asked to choose one chocolate as a token of appreciation for participating in the study. This procedure was modeled after Blechert, Michael, Vriends, Margraf, and Wilhelm (2007).

Procedure

All experimental procedures were conducted on a single day within a 1.5 hr appointment. First, a trained research assistant explained the study procedures, screened for exclusionary

criteria, and obtained informed consent. Next, participants completed baseline questionnaires using Qualtrics software. Participants were asked to observe images on a computer screen 0.91 m in front of them. They were instructed to place headphones around their neck and were told that throughout the experiment, they might hear a scream sound through a set of headphones. Participants were told to put on their headphones during differential conditioning and extinction. They were told to take off their headphones during the implicit approach avoidance training.

During habituation, participants were shown two images of each CS (CS+, CS-). The inter-trial interval (ITI) was randomized across 15, 20, and 25 s with a mean of 20 s throughout the entire experiment. The order of the CS presentation was random.

During differential conditioning, participants received 2 presentations of each CS. The final second of the CS+ coincided with a 1 s US (loud noise). The order of the CS+ and CS- was random with the exception of no more than two consecutive presentations of each CS.

Participants were then randomized to one of four groups. Group 1 (n = 37) underwent implicit approach training of the CS+ during which they approached the CS+ 90% of the time, avoided the CS+ 10% of the time, and approached/avoided the CS- at a 50-50 rate. This was achieved by pairing the CS+ and CS- image with specific backgrounds. The CS+ was presented on the background that would zoom big 90% of the time and zoom small 10% of the time, whereas the CS- was equally distributed on the zoom big and zoom small backgrounds. Group 2 (n = 35) underwent implicit avoidance training of the CS+ during which they avoided the CS+ 90% of the time, approached the CS+ 10% of the time and approached/avoided the CS- at a 50-50 rate. Group 3 (n = 36) approached and avoided the CS+ and CS- each 50% of the time. Group 4 (n = 34) completed a filler task (i.e., read a magazine) for 25 minutes, which was the average

duration of the implicit approach/ avoidance training derived from pilot testing. Participants were told not to put on their headphones during this training phase.

Next, during fear extinction phase, participants saw eight presentations of each CS without the US. The order of CS presentation followed the same randomization as in the acquisition phase. Approximately 30 min later, prior to leaving the lab, research assistants asked participants to choose one chocolate wrapped in CS+ or CS- image as a token of appreciation for participating in the experiment. Unbeknownst to the participant, this task was used as a measure of overt avoidance behavior.

Statistical analyses

Multi-level modeling with repeated measures design was conducted in Stata 13 using the mixed command for analyses on fear response during the acquisition and extinction phases. Two level growth curve models were used. Level one was trials nested within subjects. For each trial, we had CS type (CS+ or CS-) and position of trial (1-4 for acquisition, 1-8 for extinction). Position of trial was modeled as a continuous linear variable. On level 2 we included baseline characteristics (explicit avoidance, state anxiety, and trait anxiety) and group assignment (approach, avoid, 50-50, filler). Analyses were run separately for each outcome variable (US expectancy, SCR) and baseline characteristic. Baseline characteristics were modeled separately from each other because of a high correlation between state anxiety and trait anxiety, $r = .56$, $p < .001$. Modeling them separately also allowed us to limit the total number of terms in a given analysis. Models were fitted using maximum likelihood. Random effects of intercept were included in all models.

First, we investigated whether our differential fear-conditioning paradigm worked by testing two-way interactions between CS type and trial on US expectancy and SCR. We tested

these interactions separately for fear acquisition and extinction phases, giving us a total of 4 tests. At trial 1 of fear acquisition, we expected no significant difference in US expectancy and SCR between the CS+ and CS-. At trials 2-4, we expected higher US expectancy ratings and larger SCRs to the CS+ compared to the CS-. At trial 1 of extinction, we expected higher US expectancy ratings and larger SCRs to the CS+ compared to the CS-. By trial 8 of extinction, we expected no significant difference in US expectancy and SCR between the CS+ and CS-.

Next, we investigated whether group assignment moderated fear extinction response with three-way interactions between CS type, trial, and group assignment on US expectancy and SCR. When running these two tests, we used a Stata notation that treats group assignment as a categorical predictor with discrete categories. An omnibus test with 3 degrees of freedom was used to assess whether the interactions with group assignment were significant. If non-significant, we investigated a four-way interaction between CS type, trial, group assignment, and baseline characteristic on US expectancy and SCR to explore the possibility that group assignment affects certain individuals and not others.

If the four-way interactions and three-way interactions above were non-significant, we investigated whether baseline characteristics moderated fear acquisition or extinction response. We tested separate three-way interactions between CS type, trial, and each baseline characteristic on US expectancy and SCR during acquisition and extinction for a total of 12 tests. For tests on extinction response, we included group assignment as a covariate. If these interactions were non-significant, we examined all two-way interactions. We would have already reported the interaction of CS type and trial, so we only reported any significant interactions of baseline characteristics and CS type. We did not report the remaining two-way interaction of baseline characteristic and trial because we did not want to collapse across CS type in a differential fear-

conditioning paradigm. Tests of simple effects were used to explain significant interactions. Values at 1 SD below and above the mean were used to represent high anxiety/ avoidance or low anxiety/ avoidance. For analyses exploring baseline characteristics, Cohen's f^2, a measure of effect size, was calculated for statistically significant analyses. We used the method described by Selya, Rose, Dierker, Hedeker, and Mermelstein (2012). The reduced models included all covariates, main effects, and lower order interactions, whereas the full models included only the higher order interaction. Cohen's f^2 of 0.02, 0.15, and 0.35 are considered small, medium, and large effect sizes (Cohen, 1988).

Lastly, we investigated whether group assignment and each baseline characteristic predicted chocolate choice on the behavioral forced choice test. Logistic regressions were run in Stata 13 using the logit command. We tested a two-way interaction of baseline characteristic and group assignment on the probability of choosing the CS+ chocolate. If the two-way interaction was non-significant, we investigated main effects of each baseline variable and group assignment for a total of 3 tests.

Results

Tests of Differential Fear Response

US Expectancy at Acquisition. A linear mixed model revealed a significant interaction of CS type and trial on US expectancy during acquisition, $z = 11.03$, $p < .001$ (see Figure 1), such that that the slope of the CS+ across trials was positive ($z = 5.67$, $p < .001$) and the slope of the CS- was negative ($z = -4.58$, $p < .001$). Tests of simple effects revealed no significant difference in US expectancy to the CS+ and the CS- on trial 1, whereas there were higher US expectancy ratings to the CS+ than the CS- at trials 2-4, trial 1: $z = 0.28$, $p = .78$; trial 2: $z = 9.46$,

$p < .001$; trial 3: $z = 18.44$, $p < .001$; trial 4: $z = 17.96$, $p < .001$. Thus, fear of the CS+ was acquired during the acquisition phase.

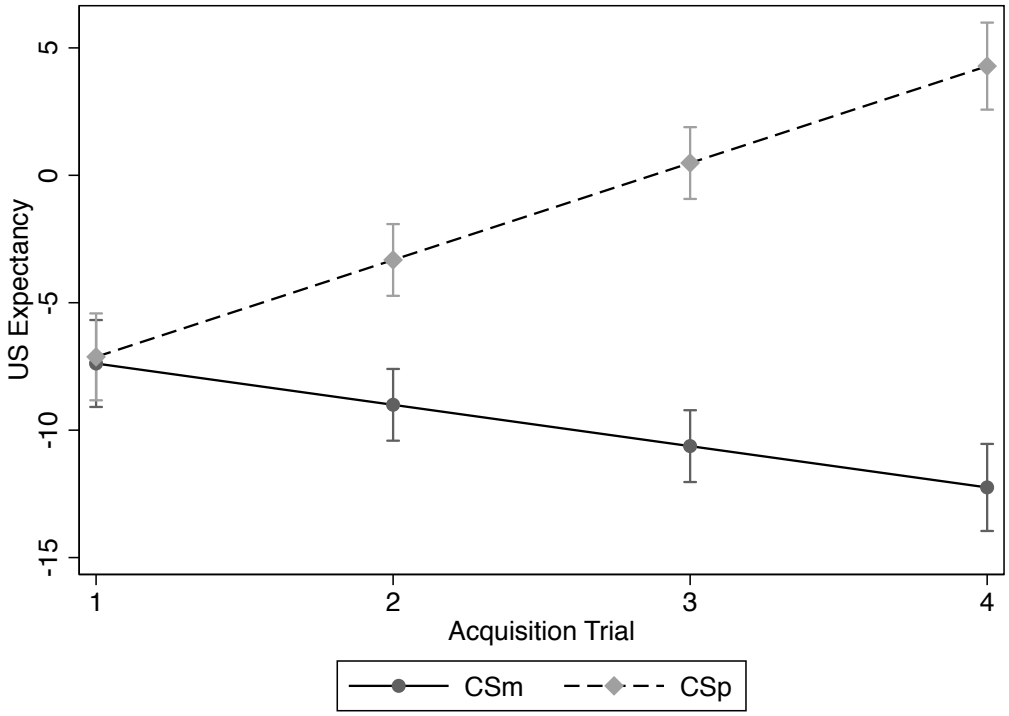

Figure 1. Predicted US expectancy ratings to the CS+ and CS- across four trials of acquisition. There was no significant difference in US expectancy to the CS+ and CS- at trial 1; however, US expectancy ratings were higher to the CS+ than CS- at trials 2-4 of acquisition.

SCR at Acquisition. A linear mixed model revealed a significant interaction of CS type and trial on SCR during acquisition, $z = 7.25$, $p < .001$ (see Figure 2), such that the slope of the CS+ across trials was positive ($z = 5.67$, $p < .001$) and the slope of the CS- was negative ($z = -4.58$, $p < .001$). Tests of simple effects revealed no significant difference in SCR following the CS+ and the CS- on trial 1, whereas there were higher SCRs to the CS+ than the CS- at trials 2-4, trial 1: $z = 0.06$, $p = .95$; trial 2: $z = 6.01$, $p < .001$; trial 3: $z = 11.93$, $p < .001$; trial 4: $z = 11.68$, $p < .001$. Thus, fear of the CS+ was acquired during the acquisition phase.

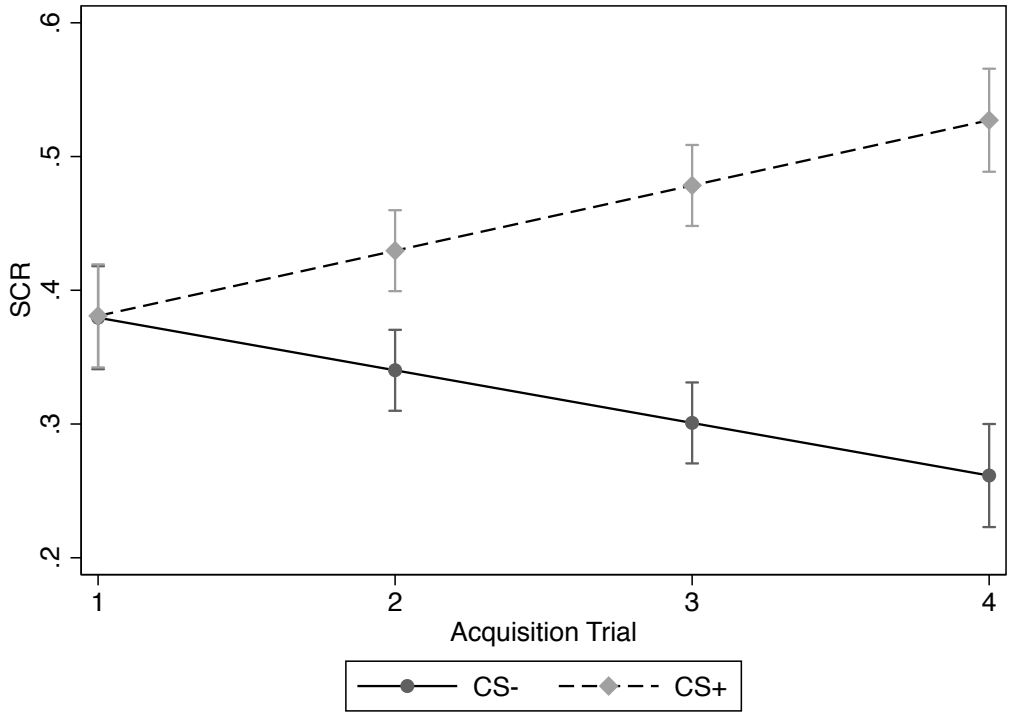

Figure 2. Predicted SCR to CS+ and CS- across four trials of acquisition. There was no significant difference in SCR between CS+ and CS- at trial 1; however, there were larger SCRs to CS+ than CS- at trials 2-4 of acquisition.

US Expectancy at Extinction. A linear mixed model revealed a significant interaction of CS type and trial on US expectancy during extinction, $z = -7.83$, $p < .001$ (see Figure 3), such that the slopes of the CS+ and CS- across trials were negative, $\beta = -2.30$, $SE = 0.10$, $z = -24.20$, $p < .001$; $\beta = -1.25$, $SE = 0.10$, $z = -13.13$, $p < .001$ respectively. Tests of simple effects revealed that there was a significant difference in US expectancy to the CS+ and the CS- at trials 1-7, but no significant difference by trial 8, trial 1: $z = 13.64$, $p < .001$; trial 2: $z = 14.52$, $p < .001$; trial 3: $z = 15.13$, $p < .001$; trial 4: $z = 14.33$, $p < .001$; trial 5: $z = 10.99$, $p < .001$; trial 6: $z = 6.55$, $p < .001$; trial 7: $z = 2.98$, $p = .003$; trial 8: $z = 0.55$, $p = .58$. Thus fear to the CS+ was extinguished during the extinction phase.

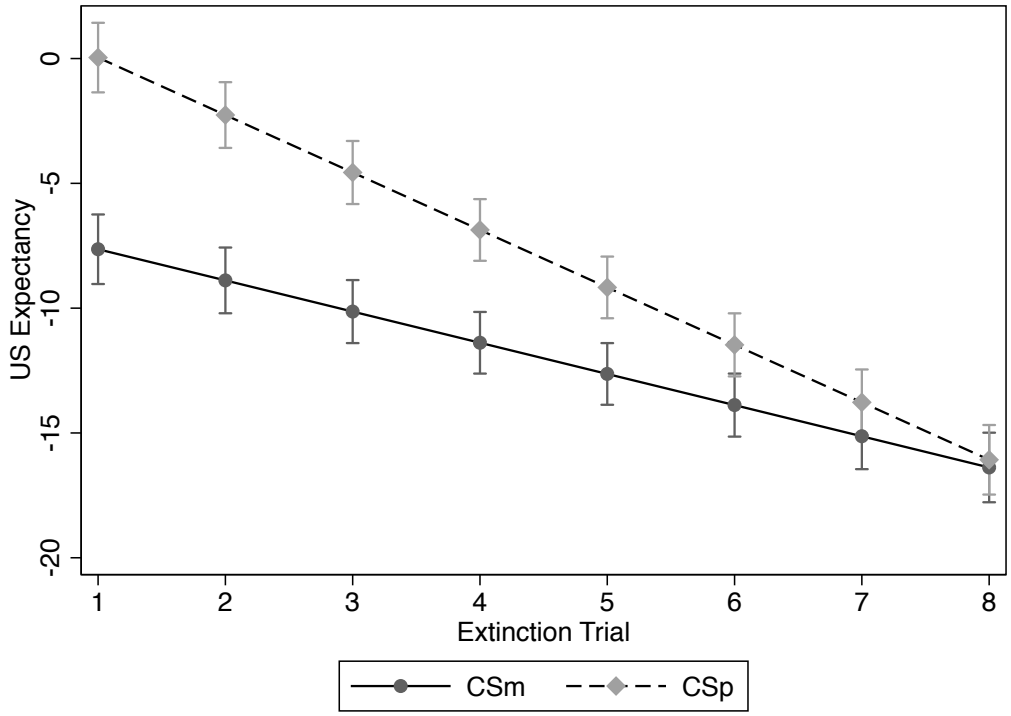

Figure 3. Predicted US expectancy ratings to CS+ and CS- across eight trials of extinction. US expectancy ratings were higher to CS+ than CS- at trials 1-7, whereas there was no significant difference at trial 8.

SCR at Extinction. A linear mixed model revealed a significant interaction of CS type and trial on SCR during extinction, $z = -2.99$, $p = .003$ (see Figure 4), such that the slopes of the CS+ and CS- across trials were negative, $\beta = -0.03$, $SE = 0.003$, $z = -9.00$, $p < .001$; $\beta = -0.01$, $SE = 0.003$, $z = -4.78$, $p < .001$ respectively. Tests of simple effects revealed that there was a significant difference in SCR to the CS+ and the CS- at trials 1-5, but no significant difference at trials 6-8, trial 1: $z = 4.51$, $p < .001$; trial 2: $z = 4.68$, $p < .001$; trial 3: $z = 4.71$, $p < .001$; trial 4: $z = 4.22$, $p < .001$; trial 5: $z = 2.95$, $p = .003$; trial 6: $z = 1.43$, $p = .15$; trial 7: $z = 0.27$, $p = .78$; trial 8: $z = -0.49$, $p = .62$. Thus, fear to the CS+ was extinguished during the extinction phase.

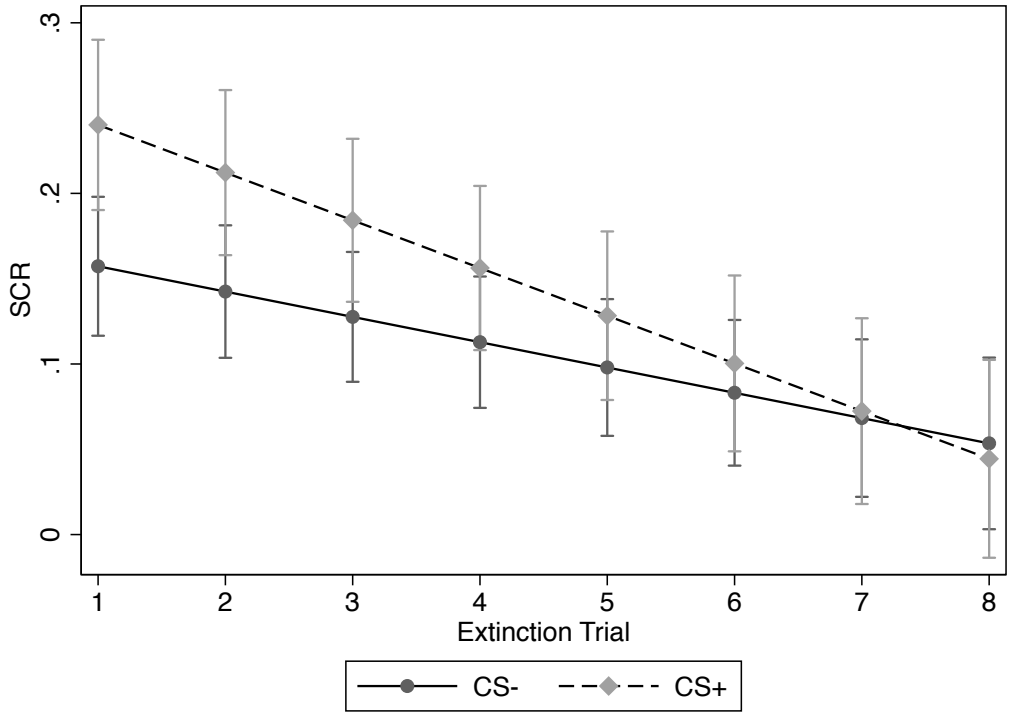

Figure 4. Predicted SCR to CS+ and CS- across eight trials of extinction. SCRs were larger to the CS+ than CS- at trials 1-5, whereas there was no significant difference at trials 6-8.

Effect of Group on Extinction

Linear mixed models revealed non-significant three-way interactions of CS type, trial, and group assignment on US expectancy and SCR during extinction *p*s > .05. The interactions continued to be non-significant when baseline characteristics were added to the interaction terms *p*s > .05.

Effect of Baseline Characteristics on Acquisition

Linear mixed models revealed non-significant three-way interactions of CS type, trial, and each baseline characteristic on US expectancy and SCR during acquisition *p*s > .05. All two-way interactions were assessed. A significant interaction between CS type and state anxiety on US expectancy emerged, $z = -3.72$, $p = .001$, $f^2 = 0.014$ (see Figure 5), such that the difference

between the CS+ and the CS- decreased as state anxiety increased. At 1 SD above the mean (high state anxiety), the difference between the CS+ and the CS- was 6.34 units ($SE = 0.77$, $z = 8.22$, $p < .001$), whereas at 1 SD below the mean (low state anxiety), the difference between the CS+ and the CS- was 10.39 units ($SE = 0.77$, $z = 13.56$, $p < .001$). Test of simple slopes revealed that the slope of the CS+ across state anxiety was not significantly different from 0 ($p = .64$), but the slope of the CS- was positive, $\beta = 0.20$, $SE = 0.08$, $z = 2.45$, $p = .014$. Thus, individuals with more state anxiety had higher US expectancy ratings to the CS- compared to individuals with less state anxiety. There were no significant three-way or two-way interactions for explicit avoidance or trait anxiety on US expectancy, ps > .05. There were also no significant three-way or two-way interactions for explicit avoidance, state anxiety, or trait anxiety on SCR, ps > .05.

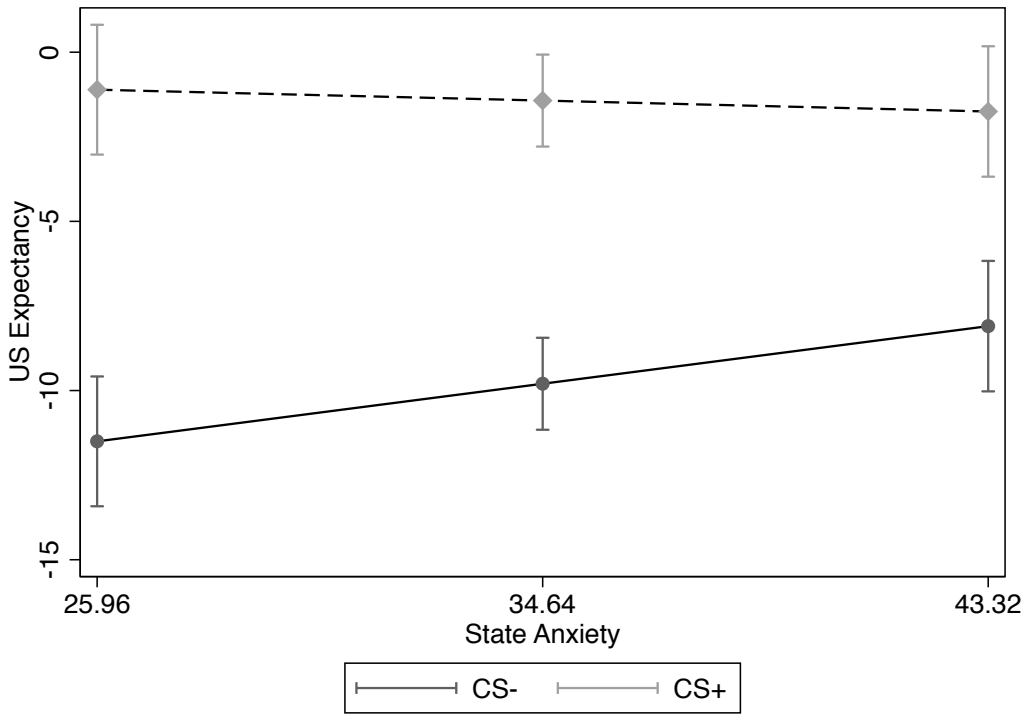

Figure 5. Predicted US expectancy ratings to CS+ and CS- for individuals with low, average, and high state anxiety. Individuals with high state anxiety had higher US expectancy ratings to the CS- than individuals with low state anxiety.

Effect of Baseline Characteristics on Extinction

Linear mixed models assessed three-way interactions of CS type, trial, and each baseline characteristic on US expectancy and SCR during extinction. Controlling for group assignment, a significant interaction of CS type, trial, and trait anxiety on US expectancy emerged, $z = 2.14$, $p = .03$, $f^2 = 0.002$ (see Figure 6), such that for low trait anxiety individuals, there was no significant difference between US expectancy to CS+ and CS- by trial 7, whereas for high trait anxiety individuals there was no significant difference between US expectancy to CS+ and CS- by trial 8, ps > .05. Test of simple slopes revealed no significant difference in the slope of the CS+ across trials for low and high trait anxiety. There was also no significant difference in the slope of the CS- across trials for individuals with low and high trait anxiety. However, linear combinations of estimators revealed that the slope of the CS+ was significantly different from the slope of the CS- across trials for individuals with low anxiety, coefficient = -1.34, $SE = 0.19$, $z = -7.01$, $p < .001$. There was also a significant difference between the slope of the CS+ and the slope of the CS- across trials for individuals with high anxiety, coefficient = -.75, $SE = 0.19$, $z = -3.86$, $p < .001$. The coefficients of the differences of slopes between CS+ and CS- were significantly different from each other for low anxiety individuals vs. high anxiety individuals, coefficient = .59, $SE = 0.27$, $z = 2.14$, $p = .03$. Therefore, the difference in slopes between CS+ and CS- is larger for individuals with low anxiety than high anxiety.

There were no significant three-way or two-way interactions for explicit avoidance or state anxiety on US expectancy, ps > .05. There were also no significant three-way or two-way interactions for explicit avoidance, state anxiety, or trait anxiety on SCR, ps > .05.

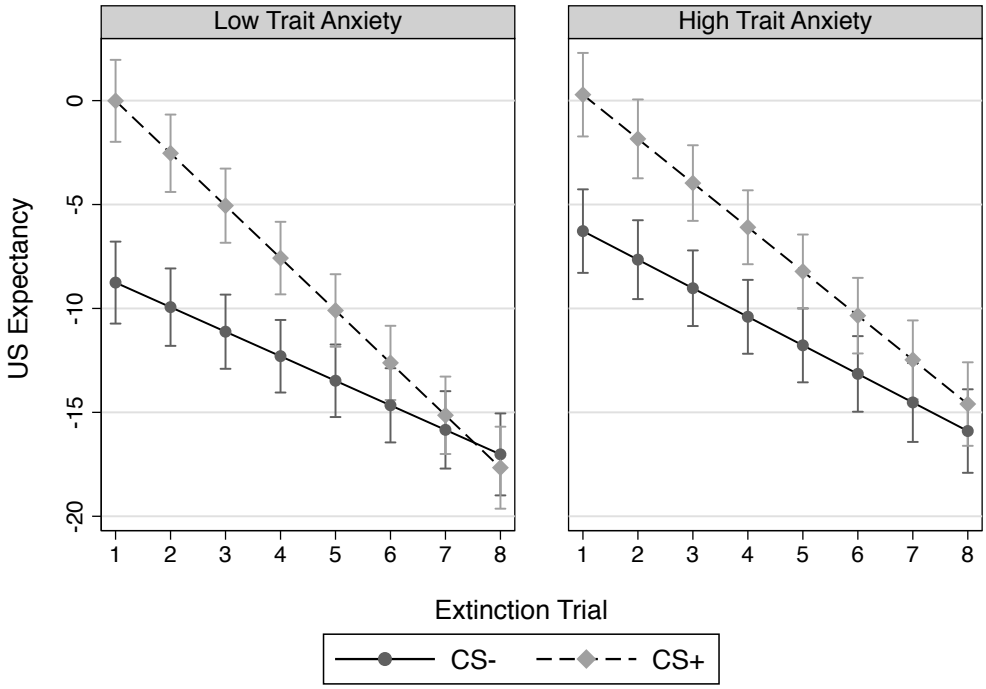

Figure 6. Predicted US expectancy ratings to CS+ and CS- for individuals with low and high trait anxiety. Individuals with low trait anxiety had no significant difference in US expectancy ratings between CS+ and CS- by trial 7, whereas individuals with high trait anxiety had no significant difference between CS+ and CS- by trial 8.

Behavioral Forced Choice Test

Logistic regressions revealed non-significant interactions of baseline characteristics and group assignment on the probability of choosing the CS+ chocolate, *p*s > .05. We then tested the main effect of baseline characteristic and group assignment within the same model. Logistic regressions revealed a significant main effect of explicit avoidance on chocolate choice, such that as avoidance increased, participants were less likely to choose the CS+ than CS-, $z = -2.35$, $SE = 0.04$, 95% CI [-0.18, -0.02], $p = .02$ (see Figure 7).

Regardless of group assignment, 80 participants chose the CS- chocolate, whereas 55 chose the CS+. One sample test of proportions revealed this rate is significantly different from 50-50, $p = .03$.

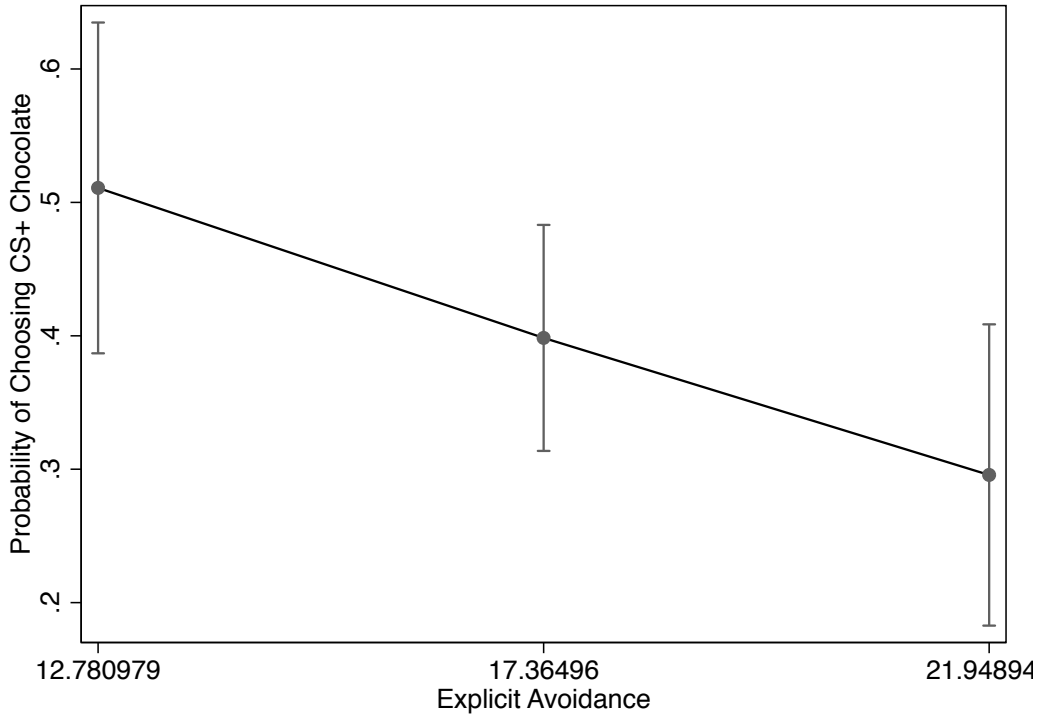

Figure 7. Greater explicit avoidance predicted less probability of choosing the CS+ chocolate compared to less explicit avoidance.

A significant main effect of state anxiety also emerged, such that as anxiety increased, participants were less likely to choose the CS+, $z = -2.04$, $SE = 0.02$, 95% CI [-0.09, -0.002], $p = .041$ (see Figure 8).

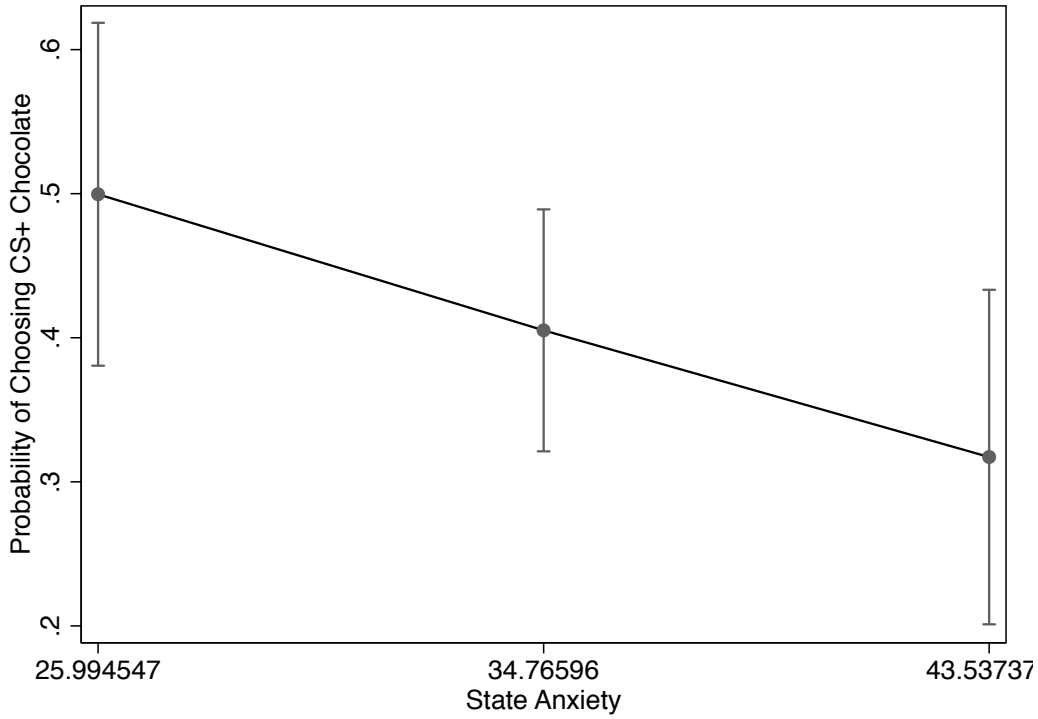

Figure 8. Higher state anxiety predicted less probability of choosing the CS+ chocolate compared to lower state anxiety

Discussion

First, the goal of the current study was to investigate the effects of manipulating implicit approach avoidance tendencies to fear stimuli on extinction performance and overt approach behavior. In line with the previous study, which aimed to manipulate implicit approach avoidance tendencies, this study did not find significant effects of approach avoidance retraining on extinction performance (Krypotos et al., 2015). We also found a non-significant effect of training on the behavioral forced choice test. Second, we aimed to expand the literature on baseline characteristics that predict acquisition performance, extinction performance, and overt avoidance behavior. We found that individuals with high explicit avoidance and high state anxiety were less likely to choose fear stimuli on a behavioral forced choice test than individuals

with low explicit avoidance and low state anxiety. Additionally, we found that individuals with high state anxiety reported higher US expectancy ratings to neutral stimuli during fear acquisition compared to individuals with low state anxiety. We also found that individuals with high trait anxiety were slower to extinguish their fear than individuals with low trait anxiety. In our sample, avoidance and anxiety did not relate to the physiological outcome of SCR. Considering the very small effect sizes of significant results it is possible that analyses with SCR were not significant simply because of inadequate power. Alternatively, anxious individuals physiological response to non-ambiguous fear stimuli may not differ from low anxious individuals, but rather, their anxiety impacts their cognitive appraisal of the situation. Previous studies have found similar effects of trait anxiety on US expectancy ratings during extinction, but not on SCR or fear potentiated startle reflex, another physiological measure of fear (Gazendam et al., 2013; Kindt & Soeter, 2014). A third explanation may be that, our sample's anxiety level may not have been high enough to see changes in physiology. In a Post Traumatic Stress Disorder sample, delayed fear extinction in SCR to CS+ was found in comparison to non-anxious individuals (Blechert, et al., 2007).

Considering that treatment for anxiety disorders includes exposure therapy, understanding what baseline characteristics make individuals more likely to approach feared stimuli may allow us to better match patients to a particular treatment. Based on our findings, avoidance may not change how individuals react to exposures, but it may predict whether they would be willing to do the exposures afterward. This would suggest that patients who are highly avoidant would benefit from treatments that explicitly explain that patients should be seeking ways to approach rather than avoid feared stimuli. Indeed, individuals with high behavioral avoidance have been found to benefit from treatments with more explicit and structured focus to

avoidance (Mesri et al., 2017). Another possible clinical implication may be that patients may benefit from altering their avoidance tendencies prior to starting exposure therapy.

Our study was limited by the fact that implicit approach or avoidance training did not have a significant effect on the behavioral forced choice test, suggesting that such training may not be able to change overt behavior after fear conditioning. On the other hand, it is possible that non-significant results may point to floor effects with responding, such that there are no added benefits of implicit training over and above regular extinction (Vansteenwegen, Crombez, Baeyens, & Eelen, 1998). Therefore, implicit training may serve useful only if there is no extinction phase. Alternatively, considering this type of training has been shown to change overt behavior in previous clinical samples of alcohol addiction, social anxiety disorder, and contamination phobia, it is also possible that fear conditioning does not engender extensive implicit avoidance as may be the case with a clinical population (Amir, Kuckertz, & Najmi, 2013; Taylor & Amir, 2012; Wiers et al., 2011). Lastly, effect sizes may have been smaller than we expected and thus we had low power with our sample size. Even though we included group assignment as a covariate in analyses, the study would benefit from replication without the manipulation component. Additionally, we found that state anxiety related to acquisition and explicit avoidance and trait anxiety to extinction. A more comprehensive measure of avoidance made by standardizing multiple measures would be beneficial moving forward. Another limitation is that all experimental procedures were conducted on the same day. Future studies would benefit from conducting follow-up procedures following a 24-hour waiting period in order to test the effects over time.

Despite limitations, this is one of few studies that investigated implicit retraining within a fear-conditioning paradigm, which may be useful in understanding underlying approach

avoidance behaviors. Additionally, this is the first study to look at explicit avoidance in a differential fear-conditioning paradigm as a predictor of future avoidance behavior, which may help understand the role of avoidance in predicting behavior after exposure therapy.

Study 2

Public Speaking Avoidance as a Treatment Moderator for Social Anxiety Disorder

A version of this work has been previously published. Below is the citation for this work.

Mesri, B., Niles, A. N., Pittig, A., LeBeau, R. T., Haik, E., & Craske, M. G. (2017). Public speaking avoidance as a treatment moderator for social anxiety disorder. *Journal of Behavior Therapy and Experimental Psychiatry, 55*, 66-72. doi:http://dx.doi.org/10.1016/j.jbtep.2016.11.010

Abstract

Background and Objectives: Cognitive behavioral therapy (CBT) and acceptance and commitment therapy (ACT) have both garnered empirical support for the effective treatment of social anxiety disorder. However, not every patient benefits equally from either treatment. Identifying moderators of treatment outcome can help to better understand which treatment is best suited for a particular patient.

Methods: Forty-nine individuals who met criteria for social anxiety disorder were assessed as part of a randomized controlled trial comparing 12 weeks of CBT and ACT. Pre-treatment avoidance of social situations (measured via a public speaking task and clinician rating) was investigated as a moderator of post-treatment, 6-month follow-up, and 12-month follow-up social anxiety symptoms, stress reactivity, and quality of life.

Results: Public speaking avoidance was found to be a robust moderator of outcome measures, with more avoidant individuals generally benefitting more from CBT than ACT by 12-month follow-up. In contrast, clinician-rated social avoidance was not found to be a significant moderator of any outcome measure.

Limitations: Results were found only at 12-month follow-up. More comprehensive measures of avoidance would be useful for the field moving forward.

Conclusions: Findings inform personalized medicine, suggesting that social avoidance measured behaviorally via a public speaking task may be a more robust factor in treatment prescription compared to clinician-rated social avoidance.

Keywords: Social anxiety; Moderator; Treatment outcome; Cognitive behavioral therapy; Acceptance and commitment therapy

Introduction

Cognitive behavioral therapy (CBT) is a well-established treatment for social anxiety disorder (Butler, Chapman, Forman, & Beck, 2006; Hofmann & Smits, 2008). Recently, acceptance and commitment therapy (ACT), a third-wave behavioral therapy, has garnered support as another effective treatment for social anxiety (Bluett, Homan, Morrison, Levin, & Twohig, 2014; Swain, Hancock, Hainsworth, & Bowman, 2013) with comparable treatment outcomes to CBT (Craske et al., 2014). Clinically significant response rates of individual patients following these interventions are around 50-55%, ranging from 43% to 70% (Craske et al., 2014; Leichsenring et al., 2014; Lincoln et al., 2005; Loerinc et al., 2015). Identifying treatment moderators may be a key to improving response rates, as they clarify for whom and under which circumstances treatments have different effects. Knowledge of such moderators can help clinicians better match patients with existing treatments from which they are likely to glean the greatest benefit (Kraemer, Wilson, Fairburn, & Agras, 2002).

Unfortunately, though several predictors of treatment outcome have been identified, little research exists on treatment moderators. This is likely due to the fact that the majority of prior studies on social anxiety disorder do not compare two active treatments, which is required for assessing treatment moderators. To our knowledge, only a few papers have reported moderators of psychological treatments for individuals with social anxiety disorder. The findings are detailed below.

In a previously published article on the current sample, individuals with social anxiety disorder who were rated as high in experiential avoidance (i.e., self-reported unwillingness to accept negative emotions) measured by the Acceptance and Action Questionnaire reported greater symptom reduction at 12-month follow-up in CBT than ACT (Craske et al., 2014). The

same pattern of moderation was found in a separate study with a mixed anxiety sample (Wolitzky-Taylor, Arch, Rosenfield, & Craske, 2012). We speculated that individuals with high experiential avoidance benefit more from CBT in the long-term because they are motivated to practice skills (e.g., exposures) designed to decrease avoidance of anxious thoughts, feelings, and sensations. Compared to CBT, ACT emphasizes acceptance rather than reducing uncomfortable internal experiences. Conversely, in the same mixed anxiety sample, individuals with high behavioral avoidance of negative physical sensations (i.e., unwillingness to continue a hyperventilation task) were more likely to benefit from ACT than CBT (Davies, Niles, Pittig, Arch, & Craske, 2015). However, this study did not examine moderators separately by diagnosis and thus it is possible that this finding was driven by patients with anxiety primarily related to bodily sensations (e.g., those with panic disorder and health anxiety), which is a common but not essential or primary component of social anxiety disorder.

A measure of avoidance that is more specific to social anxiety disorder would be avoidance of social situations. Behavioral measures of social avoidance including public speaking tasks are ecologically valid and easily implemented in research, but rarely used in clinical assessments (Beidel, Turner, Jacob, & Cooley, 1989; Hofmann, Newman, Ehlers, & Roth, 1995; Levin et al., 1993; Moscovitch, Suvak, & Hofmann, 2010). Instead, clinicians typically make judgments of behavioral avoidance based on patient self-report. However, anxious patients' estimates of their avoidance can be at odds with their actual behavior (Rachman & Lopatka, 1986; Taylor & Rachman, 1994). To our knowledge there is no previous study evaluating behavioral measures of social avoidance as moderators of treatment outcome for social anxiety disorder.

Theoretically, experiential and behavioral avoidance are two separate parts of anxiety. Whereas experiential avoidance is centered on avoidance of internal experiences such as thoughts, feelings, and physical sensation, behavioral avoidance is centered on avoidance of external experiences such as social events, public speaking, and meetings. It would seem likely that individuals who are avoidant of feared internal experiences would also be avoidant of feared external experiences. Moreover, both experiential avoidance and behavioral avoidance are indicators of poor emotion regulation (Craske, Street, & Barlow, 1989; Hayes, Wilson, Gifford, Follette, & Strosahl, 1996). From a deficit correction model, it is likely that those who show deficits in emotion regulation would benefit from a treatment that is targeting said deficit (e.g., CBT) compared to a treatment that is not targeting emotion regulation (e.g., ACT).

Given prior evidence that individuals who report high levels of experiential avoidance (indicator of poor emotion regulation) respond more positively to CBT than ACT, we hypothesized that those with the most overt social avoidance (another indicator of poor emotion regulation), would similarly respond more positively to CBT than ACT. To evaluate the effects of in vivo versus clinician-rated social avoidance, we analyzed avoidance via a public speaking task and clinician rating prior to treatment. To isolate the effect of social avoidance above social fear, we analyzed public speaking avoidance, clinician-rated social avoidance, public speaking fear, and clinician-rated social fear as moderators of all outcomes.

Method

Participants

Forty-nine individuals who met diagnostic criteria for principal or co-principal generalized social anxiety disorder using the Anxiety Disorders Interview Schedule for DSM-IV (ADIS-IV; Brown, Di Nardo, & Barlow, 1994) were included in the current analyses (see Craske

et al., 2014 for more details). Fifty-two participants completed treatment but follow-up behavioral and self-report data were missing for 3 individuals. A clinician severity rating of 4 or higher on the ADIS-IV indicated clinical severity and served as the cutoff for study eligibility. Individuals were a subset of a larger sample that included randomization to a waitlist condition (Craske et al., 2014). Because moderator analyses examine differential response to two active treatments and not differential response to active treatment versus control, we did not include participants assigned to the waitlist in these analyses. Demographics for the current subsample are in Table 1. There were no significant group differences on any demographic or diagnostic variable at baseline.

Table 1

Demographic and Clinical Characteristics of Sample

Characteristic	CBT (total = 28)	ACT (total = 24)
Gender (Female)	12	10
Reported Ethnicity		
Caucasian/ European American	14	14
Hispanic/ Latino/ Mexican	5	4
Asian-American/ Pacific Islander	7	4
Other	2	2
Age, in years	*M*=28.18 *SD*=6.54 Range: 18-43	*M*=28.78 *SD*=6.05 Range: 19-41
Education, in years	*M*=15.57 *SD*=1.93 Range: 12-18	*M*=15.33 *SD*=1.86 Range: 12-19
Marital status		
Married/ Cohabiting	4	1
Single	23	21
Other	1	2
Children (1+)	2	1
Currently on psychotropic medication	5	7
Comorbid anxiety disorder	10	11
Comorbid depressive disorder	7	7
Social anxiety disorder CSR	*M*=5.61	*M*=5.58

	SD=0.74 Range: 4-7	*SD*=1.02 Range: 4-7
Refused to do the public speaking task	2	3
LSAS-Fear	*M*=44.12 *SD*=8.21 Range: 28-62	*M*=45.30 *SD*=9.96 Range: 29-62
LSAS-Avoidance	*M*=38.01 *SD*=7.49 Range: 20-54	*M*=40.96 *SD*=13.71 Range: 14-66

Note. CBT = cognitive behavioral therapy; ACT = acceptance and commitment therapy; CSR = clinician severity rating; LSAS = Liebowitz Social Anxiety Scale

Exclusion criteria included active suicidal ideation, pregnancy, substance abuse or dependence within the last 6 months, bipolar disorder, psychosis, or certain medical diseases. Additional exclusion criteria (i.e., left handedness, metal implants, claustrophobia) were included due to a neuroimaging component. Individuals were permitted to receive concurrent psychotherapy or psychotropic medication if they were stabilized on benozodiazepines and beta blockers for a minimum of 1 month; on SSRIs, SNRIs, heterocylics, and MAO inhibitors for a minimum of 3 months; and on non-anxiety related psychotherapy for a minimum of 6 months prior to study entrance. Individuals were recruited through online and newspaper advertisements as well as community flyers and referrals from the greater Los Angeles area. The study took place at the Anxiety Disorders Research Center in the University of California, Los Angeles (UCLA).

Design

Individuals were assessed prior to treatment (i.e., pre-treatment), within 6 weeks after the end of treatment (i.e., post-treatment), 6 months after pre-treatment (i.e., 6-month follow-up), and 12 months after pre-treatment (i.e., 12-month follow-up)[1].

Treatments

Individuals in CBT and ACT groups received 12 weekly, 1-hr individual therapy sessions based on standard manuals[2]. ACT and CBT were matched on number of exposure sessions but differed in framing of the intent of exposure. CBT and ACT were administered by advanced clinical psychology students at UCLA (see Craske et al., 2014). Therapists received a two-day training session in CBT and ACT by Drs. Craske and Hayes, respectively. They received weekly group supervision by Dr. Craske and members of Dr. Craske's and Hayes's teams.

CBT. The 12-session CBT protocol has been effective for social anxiety disorder (Arch et al., 2012; Craske et al., 2014). Session 1 included assessment, psychoeducation, and self-monitoring. Sessions 2-4 covered cognitive restructuring, hypothesis testing, and breathing retraining. Session 5-11 included exposures to social stimuli. Session 12 focused on relapse prevention.

ACT. Session 1 included psychoeducation and experiential exercises. Sessions 2-3 covered creative hopelessness. Sessions 4-5 covered mindfulness, acceptance, and cognitive defusion. Sessions 6-11 honed previous skills and introduced value exploration. Exposures were used throughout to observe and accept anxiety as well as to engage in valued activities despite anxiety. Session 12 created a plan for future use of skills.

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[1] 6-month follow-up was approximately 3 months after treatment completion and 12-month follow-up was approximately 9 months after treatment completion.

[2] See authors for a copy of the CBT treatment manual (CBT manual modified from Hope, Heimberg, Juster, & Turk, 2000); the ACT manual is published (Eifert & Forsyth, 2005).

Moderator Variables

Public Speaking Avoidance and Fear. At pre-treatment, individuals were asked to give a 3-min speech in front of a video camera and two confederates. Speech topics included global warming and corporal punishment. These topics were selected to be moderate in terms of difficulty and controversy. Individuals were given 5 min to prepare the speech on one or both topics. They were instructed to rate their fear level using a 0-100 Subjective Units of Distress Scale (SUDS; Wolpe, 1990) with 0 being *no fear* and 100 being *maximum fear* at the start of the speech, at each 1-min interval, and at the end of the speech. After 3 min, individuals were given the opportunity to continue speaking for up to 3 more minutes. Mean SUDS ratings were calculated for each individual and analyzed as a measure of fear on the public speaking task. Number of minutes spoken was used as a measure of avoidance. Nine individuals who refused the public speaking task altogether were given a score of 0 min and SUDS rating of 100. See the appendix for the brief protocol used to assess public speaking avoidance.

Clinician-Rated Social Avoidance and Fear. As part of the pre-treatment ADIS-IV, clinicians rated individuals' avoidance and fear (0 = *none*, 8 = *extreme anxiety or avoidance*) of 13 social situations (e.g., dating, public speaking, speaking with unfamiliar people). Avoidance scores for all 13 situations were averaged to create a clinician-rated social avoidance score (α = .74). Fear scores for all 13 social situations were also averaged to create a clinician-rated social fear score (α = .77).

Outcome Variables

Symptom Composite Score. The self-report version of the Liebowitz Social Anxiety Scale (LSAS-SR; Fresco et al., 2001) is a 24-item measure of fear and avoidance of social and performance situations. Total ratings demonstrate good test-retest reliability (r = .83), internal

consistency (α = .95), convergent validity, and sensitivity to change following treatment (Baker, Heinrichs, Kim, & Hofmann, 2002). The Social Interaction Anxiety Scale (SIAS; Mattick & Clarke, 1998) is a 20-item measure of thoughts, feelings, and behaviors in social situations. The SIAS correlates highly with other measures of social phobia and has good internal consistency (α = .90) (Osman, Gutierrez, Barrios, Kopper, & Chiros, 1998). The Social Phobia Scale (SPS; Mattick & Clarke, 1998) is a 20-item measure of being observed by others during routine activities (e.g., eating, writing). The SPS correlates highly with other measures of social phobia and has good internal consistency (α = .91) (Osman et al., 1998). Alphas for the LSAS-SR, SIAS, and SPS were all at or above .90 in this sample across all time points (Niles, Mesri, Burklund, Lieberman, & Craske, 2013). To improve construct validity for the measurement of social anxiety severity, a composite was created from the three scales. Z-scores for each measure were combined to create a standardized measure with mean 0 and standard deviation 1. The LSAS-SR was not administered at 6-month follow-up, which includes only the SPS and SIAS.

State-Trait Anxiety Inventory. The State-Trait Anxiety Inventory – A State (STAI A-State; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983) is a 20-item measure of temporary anxiety in response to a stressor. Example items include "I feel nervous" and "I feel tense." Each item is rated on a scale from 1 (*not at all)* to 4 (*to a great extent)*. The STAI A-State demonstrates good internal consistency (α = .83 - .92) (Spielberger et al., 1983). The STAI was administered at the start of the laboratory assessment (which included a hyperventilation task, a public speaking task, and computer tasks) in order to assess stress reactivity. Because the laboratory assessment was not conducted at 6-month follow-up, STAI data were analyzed only at pre, post, and 12-month follow-up.

Quality of Life Inventory. The Quality of Life Inventory (QOLI; Frisch, 1994a, 1994b) is a measure of satisfaction with regard to 16 broad life domains. Each domain is first rated for importance on a scale from 0 (*not important*) to 2 (*extremely important)*. Then, individuals rate their life satisfaction with that domain from -3 (*very dissatisfied)* to +3 (*very satisfied)*. The QOLI demonstrates good test-retest reliability (r = .80 - .91), internal consistency (α = .77 - .89), and sensitivity to treatment change (Frisch et al., 2005).

Statistical analyses

A multi-level model with repeated measures design was used. Pre-treatment scores were modeled as a covariate rather than a repeated measure to minimize the variance in the outcome measures (Tabachnick & Fidell, 2006). This model has been previously used in examining moderators of treatment outcome (Craske et al., 2014; Niles et al., 2013; Wolitzky-Taylor et al., 2012).

Analyses were run in Stata 13 using the xtmixed command. A two level growth curve model was used. On level 1, we included Time (post-treatment, 6-month follow-up, 12-month follow-up) as a categorical predictor. On level 2, we included baseline levels of the outcome measures (as a covariate), Group (CBT or ACT), status (0 = completed 12-month measures, 1 = not completed 12-month measures), and the interactions with the moderators. To test the specificity of public speaking avoidance as a moderator above fear, we included fear during the public speaking task as a covariate. When testing public speaking fear, we included public speaking avoidance as a covariate. Pairwise correlations between public speaking avoidance and public speaking fear revealed only a moderate correlation, r = -.39, p < .001. However, pairwise correlations between clinician-rated social avoidance and clinician-rated social fear revealed a strong correlation, r = .81, p < .001. Hence, we did not include clinician-rated social fear in the

model when analyzing clinician-rated social avoidance and vice versa. Cohen's f^2, a measure of effect size, was calculated for all statistically significant models using the method described by Selya, Rose, Dierker, Hedeker, and Mermelstein (2012). Reduced models included all covariates, main effects, and two-way interactions, whereas full models added the three-way interactions. Cohen's f^2 of 0.02, 0.15, and 0.35 are considered small, medium, and large effect sizes (Cohen, 1988). Models were fitted using full maximum likelihood. Random effects of intercept were included in all models.

Because moderators may interact with Group (CBT or ACT) or Time, we tested three-way interactions between moderator, Group, and Time. If the three-way interaction was non-significant, we included Time as a covariate and tested the two-way interaction between moderator and Group. Tests of simple effects were used to explain moderation effects. More specifically, values 1 SD below and above the mean were used to represent high avoidant/ fear or low avoidant/ fear individuals. Values at 1 SD were used in order to capture representative avoidance or fear behavior in a social anxiety group, which is typical in previous moderation studies (Niles et al., 2013).

Results

As reported in Craske et al. (2014), CBT and ACT were each more effective than a waitlist comparison control for symptoms of social anxiety, with no significant differences between them.

Moderator of Symptom Composite

Public speaking avoidance significantly interacted with Group and Time to moderate symptom composite, $z = -2.49$, $p = .045$, $f^2 = 0.06$ (see Figure 1). Tests of simple effects revealed that at 12-month follow-up, more avoidant individuals (operationally defined as 1 SD above the

mean) reported .87 SD fewer symptoms following CBT than ACT, 95% CI [0.05, 1.70], z = 2.07, p = .038. No group differences were found for low avoidant individuals (1 SD below the mean), $p > .05$. Public speaking avoidance did not moderate post-treatment or 6-month follow-up, ps > .05. Neither fear on the public speaking task nor clinician-rated social avoidance or social fear were significant moderators of symptom composite at any time point, ps > .05.

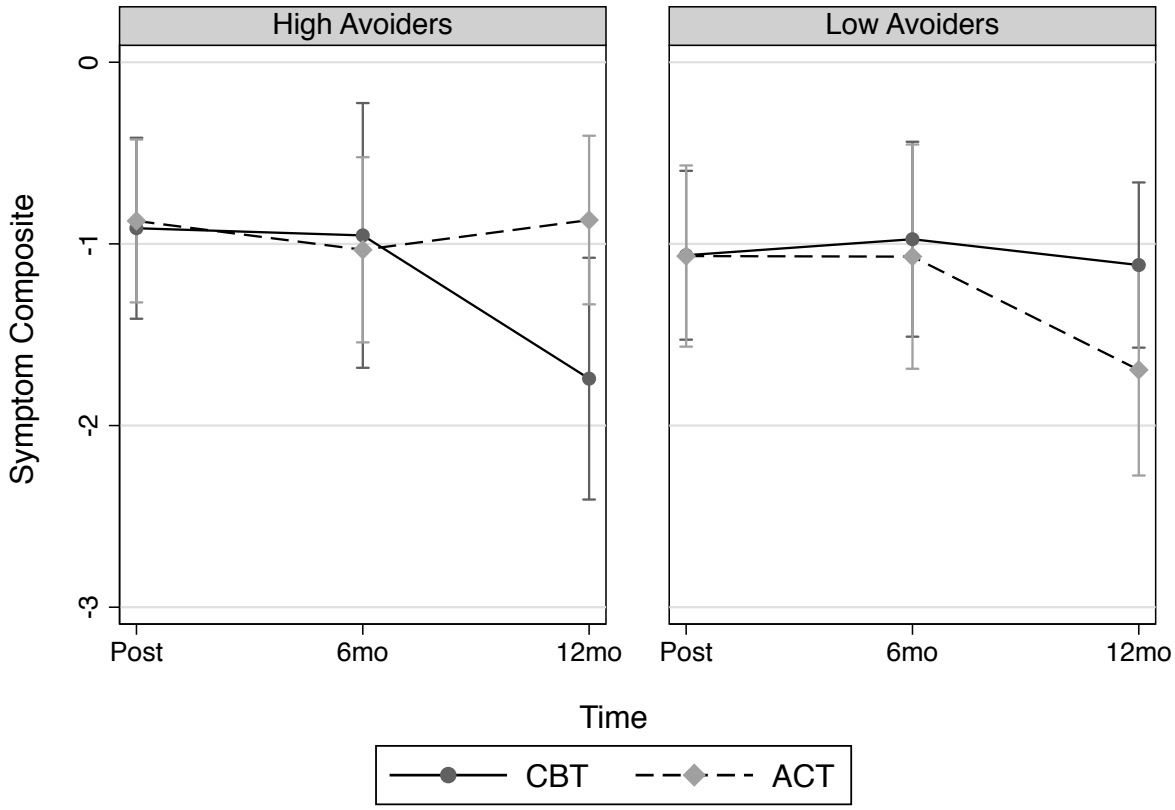

Figure 1. Public speaking avoidance significantly interacted with Group and Time to moderate symptom composite. By 12-month follow-up more avoidant individuals reported fewer symptoms following CBT than ACT. CBT = cognitive behavioral therapy; ACT = acceptance and commitment therapy

Moderator of Stress Reactivity

Public speaking avoidance significantly interacted with Group and Time to moderate stress reactivity (measured by STAI A-State prior to a stressful laboratory assessment), z = -3.87,

$p < .001, f^2 = 0.27$ (see Figure 2). Tests of simple effects revealed that at 12-month follow-up, more avoidant individuals reported 15.77 fewer points in stress reactivity following CBT than ACT, 95% CI [8.38, 23.17], $z = 4.18, p < .001$. No group differences were found for low avoidant individuals, $p > .05$. Public speaking avoidance did not moderate stress reactivity at post-treatment or 6-month follow-up, ps > .05. Neither fear on the public speaking task nor clinician-rated social avoidance or social fear were significant moderators of stress reactivity at any time point, ps > .05.

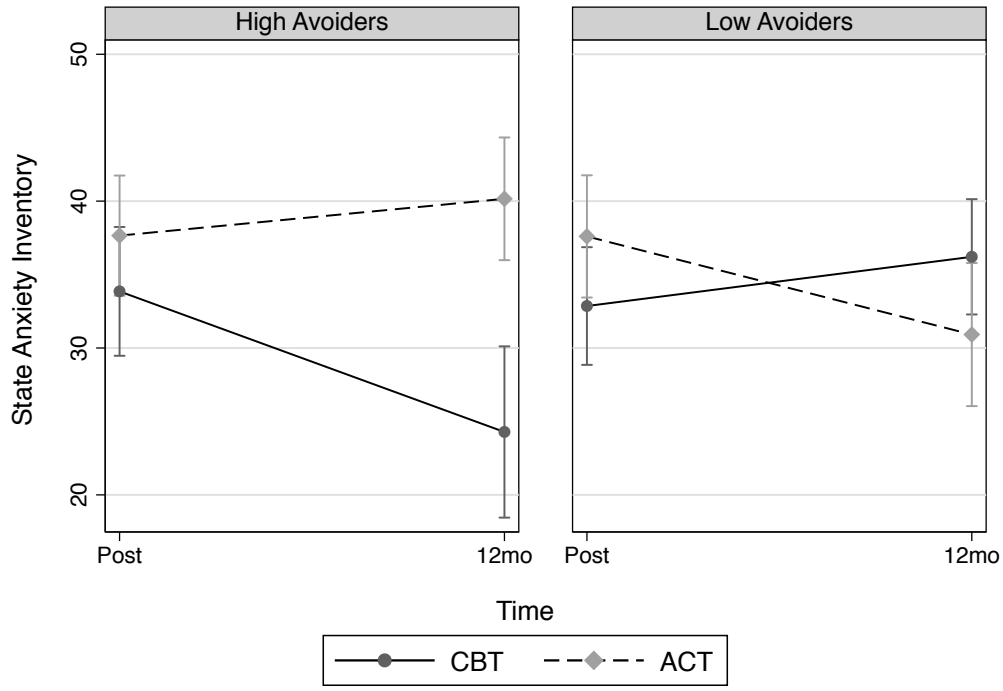

Figure 2. Public speaking avoidance significantly interacted with Group and Time to moderate stress reactivity. By 12-month follow-up, more avoidant individuals reported less stress reactivity following CBT than ACT. CBT = cognitive behavioral therapy; ACT = acceptance and commitment therapy

Moderator of Quality of Life

Clinician-rated social fear significantly interacted with Group and Time to moderate quality of life, $z = -3.21, p = .006, f^2 = 0.16$ (see Figure 3). Tests of simple effects revealed that at 6-month follow-up, less fearful individuals reported 1.32 fewer points in quality of life following

CBT than ACT, 95% CI [-2.33, -0.31], $z = -2.56$, $p = .010$ and more fearful individuals reported 1.26 more points in quality of life following CBT than ACT, 95% CI [0.003, 2.52], $z = 1.96$, $p = .049$. There were no significant differences between high and low clinician-rated fearful individuals in CBT and ACT at post-treatment and 12-month follow-up, ps > .05. Therefore, this finding is no longer discussed in this paper. Public speaking fear, public speaking avoidance, and clinician-rated social avoidance were not significant moderators of quality of life at any time point, ps > .05.

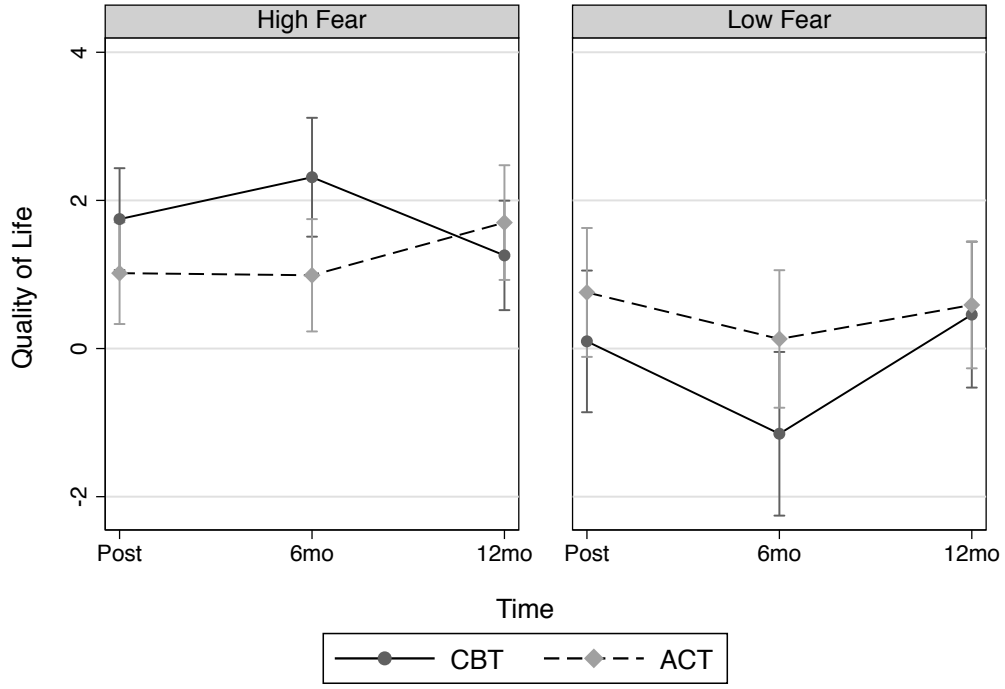

Figure 3. Clinician-rated social fear significantly interacted with Group and Time to moderate quality of life. At 6-month follow-up, less fearful individuals reported significantly lower quality of life in CBT than ACT, whereas more fearful individuals had a non-significant trend for higher quality of life in CBT than ACT. CBT = cognitive behavioral therapy; ACT = acceptance and commitment therapy

Discussion

The current study tested social avoidance as a moderator of treatment outcome for social anxiety disorder. Understanding moderators of treatment outcome allow us to better match patients to a particular treatment, which has important implications for improving treatment outcome. Our findings suggest that individuals who are more avoidant during a public speaking task benefit more, in terms of long-term symptoms and stress reactivity, from CBT than ACT.

Conversely, fear during the public speaking task did not moderate the treatment effects, suggesting that the results were specific to public speaking avoidance versus fear. Moreover, clinician-rated social avoidance did not moderate treatment effects, which could imply that the results were specific to avoidance of public speaking in particular rather than social avoidance in general. Alternatively, these results may suggest that clinicians may not be particularly accurate judges of a patient's degree of social avoidance in their daily life. Such judgments are likely to be heavily reliant on a patient's self-report, particularly at an initial assessment when the clinician has limited information about the patient, and self-report of avoidance behavior may not be an exact indicator of actual avoidance behavior in laboratory paradigms (Gamez, Kotov, & Watson, 2010; McNeil, Ries, & Turk, 1995). Another explanation for the non-significant effects of fear during the public speaking task and clinician-rated social avoidance may be low power. Power to detect an effect size of the same magnitude as those that we detected for the public speaking avoidance ranged from .74 - .86 for $f^2 = 0.27$ and .17 - .22 for $f^2 = 0.06$[3].

[3] There is a lack of statistical software to conduct power analyses for multi-level repeated measures; as an approximation, we used G*Power for linear models to calculate post hoc power analyses at alpha = .05 (Faul, Erdfelder, Lang, & Buchner, 2007). The number of predictors ranged from 10 to 13, so we calculated two values of power (more and less conservative). Because we have repeated measures, we calculated the sample size correcting for the design effect using the equation: design effect = $1 + (n-1)\rho_I$, where n = the number of time points (3) and ρ_I = intraclass correlation (Snijders & Bosker, 2012). We used the smallest and largest

We found that more avoidance on the public speaking task predicts better long-term outcome in CBT than ACT. One possible explanation is that CBT targets avoidance in a structured way through creation of an exposure hierarchy followed by in-session and homework exposure assignments. Avoidant individuals may benefit from this structure. A similar finding has been reported in a panic disorder sample that was randomly assigned to exposure therapy with an active therapist who guided patients through exposures or a less active therapist who was not present during assigned exposures (Hamm et al., 2016). Overall, panic disorder patients benefitted from exposure therapy; however, patients with greater baseline avoidance of a panic booth benefitted even more from therapist-directed exposures than self-directed exposures compared to patients who were less avoidant of the panic booth. This finding may highlight the added benefit of structure during exposures (which may be more present in CBT than ACT) for patients with high public speaking avoidance. Although ACT includes exposure, these exposures are less structured and their focus is not on fear reduction. Rather, in ACT, individuals conduct exposures in order to be present, open, mindful, and accepting of their anxious feelings with the eventual goal of taking committed action toward their values. Thus, in contrast to CBT in which exposures are a critical strategy for alleviating symptoms, the connection between exposures and treatment goals is more removed in ACT and possibly simply one of many approaches toward valued living. Indeed, there was greater adherence to behavioral exposures in CBT than ACT in the present sample (Craske et al., 2014).

Moderation was found only at the 12-month follow-up, which replicated our prior studies in the same and different samples (Craske et al., 2014; Niles et al., 2013; Wolitzky-Taylor et al.,

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intraclass correlations, to calculate a more conservative sample size of 71 and less conservative sample size of 78. Cohen's f^2 of 0.02, 0.15, and 0.35 are considered small, medium, and large effect sizes (Cohen, 1988).

2012). In prior studies, we proposed that experiential avoidance motivated continued exposure practice over the months following treatment, in turn leading to improved long-term outcomes (Wolitzky-Taylor et al., 2012). Perhaps those who were most avoidant of public speaking similarly perceived the benefits of continued exposure practice following the end of treatment resulting in better long-term outcome in CBT than ACT. It is also important to note that CBT was supervised directly by Dr. Craske and her team, whereas ACT was only supervised by Dr. Hayes's team and not himself. It is possible that if Dr. Hayes had supervised the therapists, outcomes from ACT may have differed. Moreover, more comprehensive measures of avoidance would be useful for the field moving forward.

Despite limitations, this is one of few studies that investigated moderators of ACT and CBT for social anxiety disorder. Asking patients to give a speech and identifying how long they are willing to speak may be a simple way of assessing behavioral avoidance. It may provide useful long-term prognostic information not gleaned by traditional methods such as rating levels of social avoidance based largely on patient self-report. Furthermore, should these results be replicated, they suggest that those who are more behaviorally avoidant may benefit more from CBT than ACT.

Study 3

Avoidance and Fear Moderate CBT for Panic Disorder and Agoraphobia: A Randomized Control Trial

Abstract

Cognitive behavioral therapy (CBT), a well-validated treatment for panic disorder, comprises of interoceptive exposures (i.e., exposures to panic-like physiological sensations) and/or in vivo exposures (i.e., exposures to real-world situations). Testing predictors and moderators of CBT outcomes can improve treatment efficacy. Sixty-six individuals diagnosed with panic disorder with or without agoraphobia were randomized to panic control therapy (PCT) (n = 32) or PCT and in vivo exposures (PCT + IV) (n = 34) at the Anxiety and Depression Research Center in the University of California, Los Angeles. Baseline behavioral measures of interoceptive and in vivo avoidance were tested as predictors and moderators of outcomes. Interoceptive fear, in vivo fear, demographic factors, and clinical characteristics were also tested. Diagnosticians who measured outcomes were blind to participants' treatment assignment. Multi-level models with repeated measures design revealed that individuals who displayed more in vivo avoidance, in vivo fear, and interoceptive fear fared better following PCT than PCT + IV compared to individuals who displayed less in vivo avoidance, in vivo fear, and interoceptive fear, z = 2.23, SE = 0.11, p = .03, 95% CI [0.03, 0.44], f^2 = 0.10; z = -2.81, SE = 0.14, p = .01, 95% CI [-0.65, -0.11], f^2 = 0.14; z = -2.21, SE = 0.25, p = .03, 95% CI [-1.03, -0.06], f^2 = 0.07, respectively. Results suggest that these individuals benefit from concentrated doses of exposures to their primary interoceptive concerns instead of additional in vivo exposures. Findings inform clinical decision-making and personalized medicine. Limitations include low power for detecting small effect sizes.

Keywords: panic disorder, agoraphobia, predictor, moderator, cognitive behavioral therapy

Introduction

Panic disorder, which is characterized by fear that panic attacks will lead to catastrophic consequences (e.g., heart attack), is highly comorbid with agoraphobia (APA, 2013; Kessler et al., 2006). Agoraphobia is characterized by fear and avoidance of places (e.g., concerts) that are hard to escape in the event of panic-like or other incapacitating symptoms (APA, 2013). Exposure-based therapies such as cognitive behavioral therapy (CBT) are considered gold standard treatments for both panic disorder and agoraphobia (Hofmann, Asnaani, Vonk, Sawyer, & Fang, 2012; Mitte, 2005; Moscovitch, Antony, & Swinson, 2009). Despite a large amount of support for CBT, a recent systematic review found that 53% of individuals who were diagnosed with both panic disorder and agoraphobia did not achieve clinically significant improvement following CBT (Loerinc et al., 2015). A review of four studies on panic disorder without agoraphobia found that 28% of participants did not achieve clinical improvement (Siev & Chambless, 2007). One way to increase the efficacy of CBT is to test predictors and moderators of treatment outcomes (Marks, 2002; Shoham & Insel, 2011). Predictors elucidate which individuals have the lowest response rates and moderators clarify whether certain individuals benefit more from one treatment or another (Insel, 2009).

The most commonly tested predictors of treatment outcomes are demographic factors, yet it appears that these have little predictive power (Kraemer, Wilson, Fairburn, & Agras, 2002; Porter & Chambless, 2015; Schneider, Arch, & Wolitzky-Taylor, 2015). No conclusions have been made about whether demographic factors moderate responses to treatment because of the dearth of such studies. This may be because moderation analyses require studies that compare two or more active treatments as opposed to studies that compare a single active treatment and a non-active control (Kraemer et al., 2002).

Nevertheless, previous research has shown that clinical factors (e.g., duration of episode, age of onset) predict outcomes. From their review of five studies, Porter and Chambless (2015) concluded that individuals with older age of onset and shorter duration of panic disorder fared better in CBT compared to individuals with younger age of onset and longer duration of panic disorder. To our knowledge, only two studies investigated clinical factors as moderators of CBT outcomes. Dow et al. (2007) found that individuals whose last panic episodes were longer fared better after 12 weeks of CBT than 6 weeks of CBT compared to individuals whose episodes were shorter. Unlike the aforementioned study, age of onset was not a significant moderator. On the other hand, El Alaoui et al. (2013) found that individuals with later onsets of panic disorder fared better after internet-CBT than group-CBT compared to individuals with earlier onsets. Considering the limited research on clinical characteristics as moderators of CBT outcomes, no definitive conclusions can be made in terms of their role in treatment prescription.

In addition to demographic and clinical factors, theory-driven predictors and moderators can be investigated (Kraemer et al., 2002). A central theoretical factor in the diagnosis, maintenance, and treatment of panic disorder and agoraphobia is avoidance (Craske & Barlow, 1988). Interoceptive avoidance refers to avoidance of panic-like physiological sensations (e.g., racing heart, shortness of breath), whereas in vivo (or agoraphobic) avoidance refers to avoidance of situations (e.g., crowds) or places (e.g., malls). In a systematic review, Porter and Chambless (2015) reported that baseline in vivo avoidance was the most consistent predictor of response to CBT for panic disorder with or without agoraphobia. Specifically, individuals with greater in vivo avoidance did worse following CBT compared to those with less avoidance. Consequently, it is important to test whether these individuals respond better to different type of treatment. It is also important to elucidate the role of interoceptive rather than in vivo avoidance.

To our knowledge, only two studies on panic disorder or agoraphobia have tested whether baseline avoidance moderates treatment outcomes between two different types of CBT. Both of these studies are limited to measures of in vivo avoidance. Dow et al. (2007) found that baseline self-reported in vivo avoidance did not moderate treatment efficacy between 12-week and 6-week CBT. In contrast, Hamm et al. (2016) found that avoidance, measured using a behavioral avoidance test rather than self-report, moderated response to exposure therapy. As part of a multi-site randomized control trial (RCT), 301 individuals with panic disorder and agoraphobia were randomized to (a) exposure therapy accompanied by a therapist or (b) exposure therapy that was not accompanied by a therapist. At baseline, participants were asked to enter a panic booth (small, dark, enclosed chamber) for 10 min. Of the 226 individuals who had complete data, individuals who were avoidant of the panic booth did better following therapist accompanied exposures than non-accompanied ones. It was theorized that avoidant individuals benefit from a treatment that more actively and systematically targets that avoidance. This finding suggests that in vivo avoidance can be used to better match individuals to treatment.

The goal of the present study was to investigate both in vivo and interoceptive avoidance as predictors and moderators of treatment outcomes. In the primary outcome paper, Craske, DeCola, Sachs, and Pontillo (2003) found that two different types of CBT were equally efficacious for panic disorder and agoraphobia. From a deficit correction perspective and in line with previous findings (e.g., Hamm et al., 2016), we hypothesized that individuals who are more avoidant of interoceptive cues would benefit more from CBT that emphasizes interoceptive exposures, compared to individuals who are less avoidant of interoceptive cues. Additionally, we hypothesized that individuals who are more avoidant of in vivo situations would benefit more from CBT that emphasizes in vivo exposures, compared to individuals who are less avoidant of

in vivo situations. We also tested whether fear (controlling for avoidance), clinical characteristics, and demographic characteristics predicted or moderated treatment outcomes.

Method

Design

Individuals were assessed prior to treatment (i.e., pre-treatment), after 8 weeks of starting treatment (i.e., mid-treatment), after 16 weeks of starting treatment (i.e., post-treatment), and 6 months after post-treatment (i.e., 6-month follow-up).

Participants

Seventy-seven individuals with a principal diagnosis of panic disorder with or without agoraphobia were assessed as part of an RCT at the Anxiety and Depression Research Center in the University of California, Los Angeles (see Craske et al., 2003 for more details). Participants were recruited via radio advertisements and community referrals. Informed consent was obtained upon study enrollment. Independent diagnosticians used a semi-structured interview, the Anxiety Disorders Interview Schedule (ADIS-IV; Brown, Di Nardo, & Barlow, 1994) for the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; APA, 1994).

Half of the participants were randomized with 1:1 allocation ratio to 16 weeks of panic control therapy (PCT), whereas the other half was randomized to eight weeks of PCT followed by eight weeks of therapy focused on in vivo exposures (PCT + IV). Of the 77 individuals who enrolled in the study, 9 dropped out prior to starting treatment and 2 were removed from the study (see Craske et al., 2003 for more details). Table 1 includes baseline demographic characteristics of the remaining 66 individuals.

Table 1

Subsample Baseline Demographic and Clinical Characteristics by Treatment Group

Treatment group	PCT (*n* = 32)	PCT + IV (*n* = 34)
Gender		
Female	17	22
Male	15	12
Ethnicity		
Caucasian/European American	24	22
Hispanic/Latino/Mexican	1	6
African American/Black	2	2
Asian American/Pacific Islander	2	0
American Indian/Alaskan	0	0
Other	1	1
Age, in years	*M* = 38.10 *SD* = 9.36 Range: 18 – 53	*M* = 32.33 *SD* = 9.86 Range: 18 – 54
Education, in years	*M* = 15.10 *SD* = 2.45 Range: 12 – 18	*M* = 15.27 *SD* = 1.94 Range: 12 – 18
Psychotropic medication		
Current use	14	12
History of use	8	11
Never used	10	11
Duration in years since first panic attack	*M* = 10.10 *SD* = 10.08 Range: 0.58 – 36	*M* = 7.02 *SD* = 9.11 Range: 0.58 – 36
Age of onset	*M* = 28.47 *SD* = 11.68 Range: 8 – 47.75	*M* = 25.36 *SD* = 9.68 Range: 13 – 47.75
Panic disorder CSR	*M* = 5.94 *SD* = 0.67 Range: 5 – 7	*M* = 5.91 *SD* = 0.79 Range: 5 – 7
Agoraphobia		
None to mild	5	6
Moderate to severe	26	28

Note. Subsample sizes do not always add up to the total number in each group because of missing data for certain variables. CSR = clinical severity rating. Data were Winsorized at the 1st and 99th percentiles.

Exclusion criteria included psychosis, current substance use disorder, bipolar disorder, organic brain damage, pregnancy, severe medical conditions, and asthma. Individuals were permitted to use concurrent psychotropic medication if they had stabilized on their dosage and agreed to maintain that dosage through post-treatment. They were permitted to receive concurrent psychotherapy if the therapy (a) did not target panic disorder or agoraphobia, (b) began more than 6 months prior to study enrollment, and (c) was maintained through post-treatment. Participants were excluded if they received CBT for panic disorder or agoraphobia within 2 years prior to enrolling in the study.

Treatments

All participants received 16 weekly (90 min) group CBT sessions consisting of 3-5 patients and 2 therapists (see Craske et al., 2003 for more details). Therapists were graduate students and post-doctoral fellows trained by Dr. Craske.

For all participants, the first eight sessions comprised of PCT, a well-supported manualized treatment for panic disorder and agoraphobia (Barlow, Craske, Cerny, & Klosko, 1989; Craske & Barlow, 2007). PCT includes psychoeducation, breathing retraining, cognitive restructuring, and interoceptive exposures. Interoceptive exposures include engaging in activities that induce panic-like physiological symptoms (e.g., hyperventilating). Participants were also encouraged to go to places or engage in activities that activate physiological concerns (e.g., exercising).

For sessions 9-16, the PCT group repeated the first eight sessions, except that at session 9, they were encouraged to conduct in vivo exposures if they thought that such exposures would be beneficial. In vivo exposures include going to places that do not inherently induce panic

sensations, but where escaping or receiving help is difficult in the event of panic-like or other incapacitating symptoms (e.g., crowded concert). They were not given specific instructions or feedback on implementing in vivo exposures. In contrast, the PCT + IV group spent sessions 9-16 focused on in vivo exposures. Participants made a new fear hierarchy and were instructed on applying panic control techniques (i.e., breathing retraining, cognitive restructuring, interoceptive exposures) to in vivo exposures. As reported in Craske et al. (2003), therapist adherence to protocol was 5.52 for PCT and 5.49 for PCT + IV on a scale from 1 *(no adherence)* to 7 (*extensive adherence*).

Predictors and Moderators

Interoceptive avoidance and fear. At baseline, participants engaged in three counterbalanced interoceptive tasks: hyperventilating (i.e., deep and rapid breathing) for up to 60 s, spinning (i.e., standing and turning once every 3 s) for up to 90 s, and tube breathing (i.e., restricted breathing through a small tube) for up to 120 s (Lee et al., 2006; Schmidt & Trakowski, 2004). Durations were all positively correlated and were summed after being divided by the maximum per task: hyperventilating and spinning, $r_s(66) = .65$, $p < .001$; hyperventilating and tube breathing, $r_s(66) = .24$, $p = .05$; tube breathing and spinning, $r_s(66) = .40$, $p = .001$. One participant who refused to do the tube breathing received a time of 0 s.

To distinguish avoidance from fear, participants rated their anticipatory fear before each task and their maximum fear during each task on scales from 0 *(not at all)* to 8 (*extreme*). We averaged the anticipatory and maximum ratings because they were moderately or strongly correlated: hyperventilating, $r_s(66) = .45$; spinning $r_s(66) = .66$; tube breathing $r_s(66) = .51$, ps < .001. Then, ratings were averaged across the tasks because they were moderately to strongly correlated: hyperventilating and spinning, $r_s(66) = .72$; hyperventilating and tube breathing,

$r_s(66) = .59$; tube breathing and spinning, $r_s(66) = .60$, ps $< .001$. Table 2 includes means, standard deviations, and ranges for interoceptive avoidance and fear by treatment group.

In vivo avoidance and fear. In vivo avoidance and fear were measured via panic booth behavioral task and diagnostician rating. We did not combine these measures because of weak correlations: panic booth and diagnostician-rated avoidance, $r_s(60) = .28$, $p = .03$; panic booth and diagnostician-rated fear, $r_s(62) = .39$, $p < .002$. Table 2 includes means, standard deviations, and ranges for in vivo avoidance and fear by treatment group.

Panic booth avoidance and fear. At baseline, participants entered a panic booth (i.e., 2 ft x 3 ft x 7 ft dark, enclosed space with a door that could not be opened from the inside) for up to 10 min, with longer durations indicative of less avoidance (e.g., Hamm et al., 2016). Six individuals who refused received a time of 0 min. To distinguish avoidance from fear, participants rated their anticipatory fear before the task as well as their maximum fear during the task on a scale from 0 *(not at all)* to 8 (*extreme*). We averaged anticipatory and maximum fear because they were strongly correlated, $r_s(63) = .76$, $p < .001$.

Diagnostician-rated in vivo avoidance and fear. As part of the baseline ADIS-IV, diagnosticians rated participants' avoidance and fear of 22 in vivo situations on a scale from 0 (*no avoidance or escape/ no apprehension*) to 8 (*very severe: never enters even with safe person/ very severe apprehension*). Separate sums for avoidance and fear were used. We cannot report the internal consistency of these ratings because we are missing the raw data.

Table 2

Subsample Baseline Avoidance and Fear Ratings by Treatment Group

Treatment group	PCT (n = 32)	PCT + IV (n = 34)
Sum of interoceptive duration (0-3)	M = 2.61	M = 2.67

	SD = 0.48 Range: 1.10 – 3	*SD* = 0.44 Range: 1.38 – 3
Interoceptive average fear (0-8)	*M* = 3.35 *SD* = 1.81 Range: 0.5 – 7.17	*M* = 3.90 *SD* = 1.89 Range: 0.33 – 7.17
Panic booth duration in min (0-10)	*M* = 8.25 *SD* = 3.49 Range: 0 – 10	*M* = 8.51 *SD* = 3.51 Range: 0 – 10
Panic booth average fear (0-8)	*M* = 3.66 *SD* = 2.76 Range: 0 – 8	*M* = 4.48 *SD* = 2.59 Range: 0 – 8
Sum of diagnostician-rated in vivo avoidance (0-176)	*M* = 42.95 *SD* = 26.20 Range: 4 – 97	*M* = 45.81 *SD* = 38.40 Range: 4 – 127
Sum of diagnostician-rated in vivo fear (0-176)	*M* = 56.05 *SD* = 25.75 Range: 9 – 112	*M* = 55.92 *SD* = 35.42 Range: 9 – 127

Note. Data were Winsorized at the 1st and 99th percentiles.

Demographic and clinical characteristics. At baseline, participants completed questionnaires with demographic characteristics. Gender (1 = male, 2 = female) and ethnicity (1 = Caucasian/European American, 2 = Hispanic/Latino/Mexican, 3 = African American/Black, 4 = Asian American/Pacific Islander, 5 = American Indian/Alaskan, 6 = other) were coded as categorical variables. For analyses, we used a categorical measure of ethnicity (1 = Caucasian, 2 = not Caucasian) because 75.41% of the sample was Caucasian. Age in years and education (i.e., highest grade completed) were coded as continuous variables. Diagnosticians collected the following characteristics during the ADIS-IV: use of psychotropic medication as a categorical variable (1 = current use, 2 = history of use, 3 = never used psychotropic medication); duration in years since first panic attack as a continuous variable; and age of onset (i.e., baseline age minus duration in years since first panic attack) as a continuous variable. See Table 1 for specific values of demographic and clinical characteristics.

Outcome Variables

Independent diagnosticians who were blind to treatment conditions administered the ADIS-IV at baseline, mid-treatment, post-treatment, and 6-month follow-up. Outcome measures for the current set of analyses come from the ADIS-IV.[4]

Panic disorder. Diagnosticians rated three measures of panic disorder on the ADIS-IV: (a) frequency of panic attacks per month, (b) participant's apprehension of having a panic attack on a scale from 0 (*not at all*) to 8 (*extreme*), and (c) clinical severity rating (CSR) of distress and disablement on a scale from 0 (*not at all*) to 8 (*extreme*) for panic disorder. CSRs of 4 or higher represent a clinically significant condition. The ADIS-IV has good to excellent diagnostic reliability for panic disorder with or without agoraphobia (κ = .72 - .79) and excellent inter-rater reliability for panic disorder CSR (κ = .83) (Brown, Di Nardo, Lehman, & Campbell, 2001).

Agoraphobia. In the agoraphobia section of the ADIS-IV, diagnosticians rated the severity of distress and disablement for agoraphobia on scales from 0 (*not at all*) to 8 (*extreme*). The average of the two ratings was used because they were strongly to very strongly correlated: pre-treatment, $r_s(58) = .72$; mid-treatment, $r_s(47) = .98$; post-treatment, $r_s(40) = 1.00$; 6-month follow-up, $r_s(27) = 1.00$, $ps < .001$.

Statistical Analyses

Outliers on all continuous variables (i.e., values less than 1% or greater than 99%) were replaced with the nearest non-outlier value based on the Winsor method (Tukey, 1962). Less than two percent of the data were Winsorized.

Multi-level models with repeated measures design were run in Stata 13 using the mixed command. On level 1, we included time (post-treatment, 6-month follow-up) as a categorical variable. On level 2, we included group (PCT, PCT + IV) and predictors/ moderators (all main

[4] Self-report outcome measures were not analyzed because more than 50% of participants did not return questionnaires. These measures were also excluded from the primary outcome paper.

effects and interactions). Pre-treatment and mid-treatment scores were modeled as covariates rather than repeated measures to minimize the variance in the outcome measures (Tabachnick & Fidell, 2006). This model has been previously used in examining moderators of treatment outcomes (e.g., Craske et al., 2014; Niles, Mesri, Burklund, Lieberman, & Craske, 2013).

To test the specificity of avoidance as a predictor or moderator over and above fear, we included fear on that task as a covariate (level 2). To test the specificity of fear over and above avoidance, we included avoidance on that task as a covariate (level 2). We did this only if there was enough non-shared variance between the two variables, which was the case for interoceptive and panic booth avoidance and fear, but not for diagnostician-rated avoidance and fear.[5]

Shapiro-Wilk tests revealed normally distributed histograms of residuals for all models except for those that included gender and apprehension of having a panic attack. Residuals were not normalized even after transformations and thus are not reported. Models were fitted using maximum likelihood to use all available data (Snijders & Bosker, 2012). Random effects of intercept were included in all models.

According to guidelines for moderation analyses, putative moderators should not be related to treatment group (Kraemer et al., 2002). Individuals who received PCT were significantly older (M = 38.10, SD = 9.36) than those who received PCT + IV (M = 32.33, SD = 9.86), $t(62) = -2.40$, $p = .02$. Consequently, age was not tested as a moderator. Age was included as a covariate for analyses that included frequency of panic attacks because of significant negative relationships between age and frequency at post-treatment, $r_s(48) = -.35$, $p = .02$ and 6-month follow-up, $r_s(38) = -.33$, $p = .04$.

[5] Interoceptive avoidance and fear: 16% shared variance, $r_s(66) = .40$
Panic booth avoidance and fear: 31% shared variance, $r_s(63) = .56$
Diagnostician-rated in vivo avoidance and fear: 74% shared variance, $r_s(63) = .86$.

Per Schneider et al. (2015) recommendation, we tested both quadratic (i.e., non-linear) and linear effects of moderators. We conducted tests in the following order until one was statistically significant ($p < .05$) or all tests had been conducted: (a) interaction of quadratic moderator (i.e., moderator^2) × group × time, (b) moderator^2 × group (time = covariate), (c) moderator × group × time, (d) moderator × group (time = covariate), (e) predictor × time (group = covariate), (f) predictor (group & time = covariates). Tests of instantaneous slope were conducted for quadratic models and tests of simple slopes for linear models. Bonferroni corrections were used for tests of simple effects and slopes in analyses related to demographic and clinical characteristics because of the lack of theory behind those analyses.

Cohen's f^2, a measure of effect size, was calculated for all statistically significant models using the method described by Selya, Rose, Dierker, Hedeker, and Mermelstein (2012). Reduced models included all covariates, main effects, and lower order interactions, whereas full models also included the higher order interaction. Cohen's f^2 of 0.02, 0.15, and 0.35 are considered small, medium, and large effect sizes (Cohen, 1988).

To calculate post hoc power, we used G*Power for linear models as an approximation because there is no statistical software for multi-level repeated designs (Faul, Erdfelder, Lang, & Buchner, 2007). The power to detect a large effect size ($f^2 = 0.35$) ranged from .90 to 1.00, medium ($f^2 = 0.15$) from .49 to .91, small to medium ($f^2 = 0.085$) from .27 to .65, and small ($f^2 = 0.02$) from .09 to .17; thus, we were sufficiently powered to detect large and potentially medium effect sizes and underpowered for smaller ones.[6]

[6] To calculate a range of power, we used the smallest and largest number of predictors (5 for analyses that included a predictor without time and 9 for analyses that included a quadratic moderator without time). We also used the sample size of 66 and a less conservative size of 117 that takes into consideration the added benefit of a repeated measures design. To calculate the sample size correcting for the design effect we used the equation: design effect = $1 + (n-1)\rho_I$,

Results

As reported in Craske et al. (2003), treatments did not differ significantly at post-treatment or 6-month follow-up on any outcome measures (i.e., frequency of panic attacks per month, apprehension of having a panic attack, avoidance/ fear of interoceptive tasks, avoidance/ fear of panic booth, diagnostician-rated in vivo avoidance, severity of agoraphobia, functioning).

Interoceptive Avoidance and Fear

Controlling for interoceptive fear, interoceptive avoidance did not moderate panic disorder outcomes, *p*s > .05. Controlling for interoceptive avoidance, interoceptive fear significantly interacted with group to moderate apprehension of having a panic attack, $z = -2.21$, SE = 0.25, $p = .03$, 95% CI [-1.03, -0.06], $f^2 = 0.07$ (see Figure 1). Individuals who reported more interoceptive fear (i.e., 2 SD above the mean) had 2.49 units fewer in apprehension of having a panic attack after PCT than PCT + IV, $z = 2.49$, SE = 1.01, $p = .014$, 95% CI [0.40, 4.48]. Moreover, individuals who reported the maximum interoceptive fear (8) had 2.85 units fewer in apprehension of having a panic attack after PCT than PCT + IV, $z = 2.85$, SE = 1.16, $p = .014$, 95% CI [0.57, 5.13]. The slope of the PCT group was negative, $z = -2.20$, SE = 0.20, $p = .03$, 95% CI [-0.82, -0.05], whereas the slope of the PCT + IV group was not significantly different from zero, $p = .51$. This reveals that individuals with greater interoceptive fear benefitted more from PCT than PCT + IV. Interoceptive fear did not moderate other panic disorder outcomes (i.e., frequency of panic attack, CSR).

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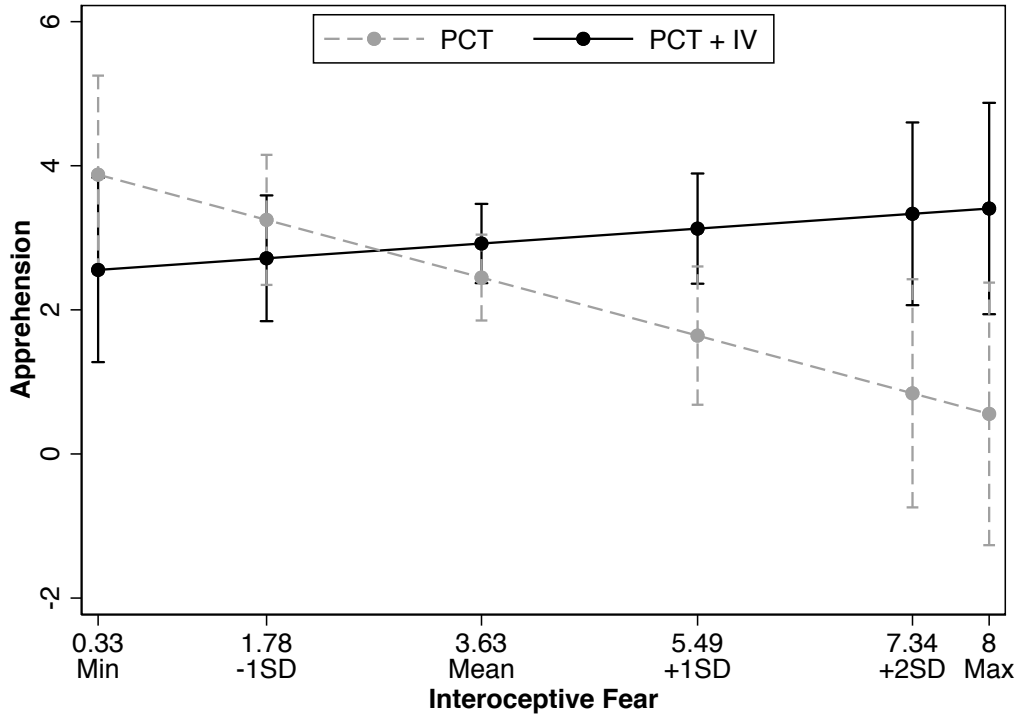
where n = the number of time points (i.e., 2) and ρ_I = intraclass correlation (Snijders & Bosker, 2012). We used the smaller intraclass correlation from our analyses, which was .13 and we set alpha at .05.

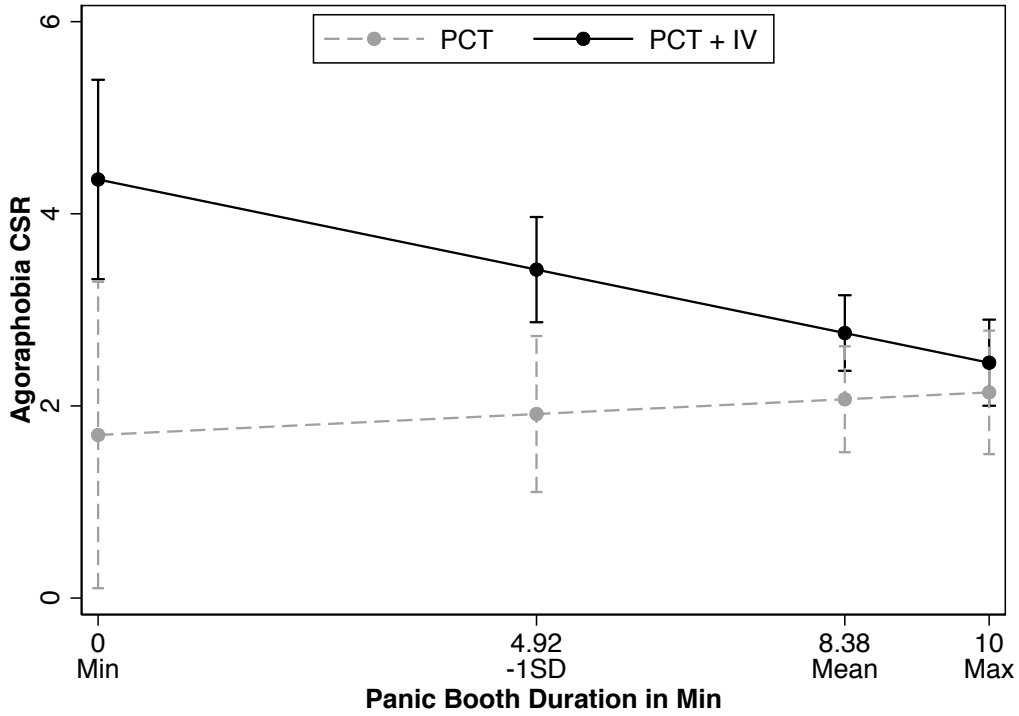
Figure 1. Baseline interoceptive fear significantly interacted with group to moderate apprehension of having a panic attack.



Panic Booth Avoidance and Fear

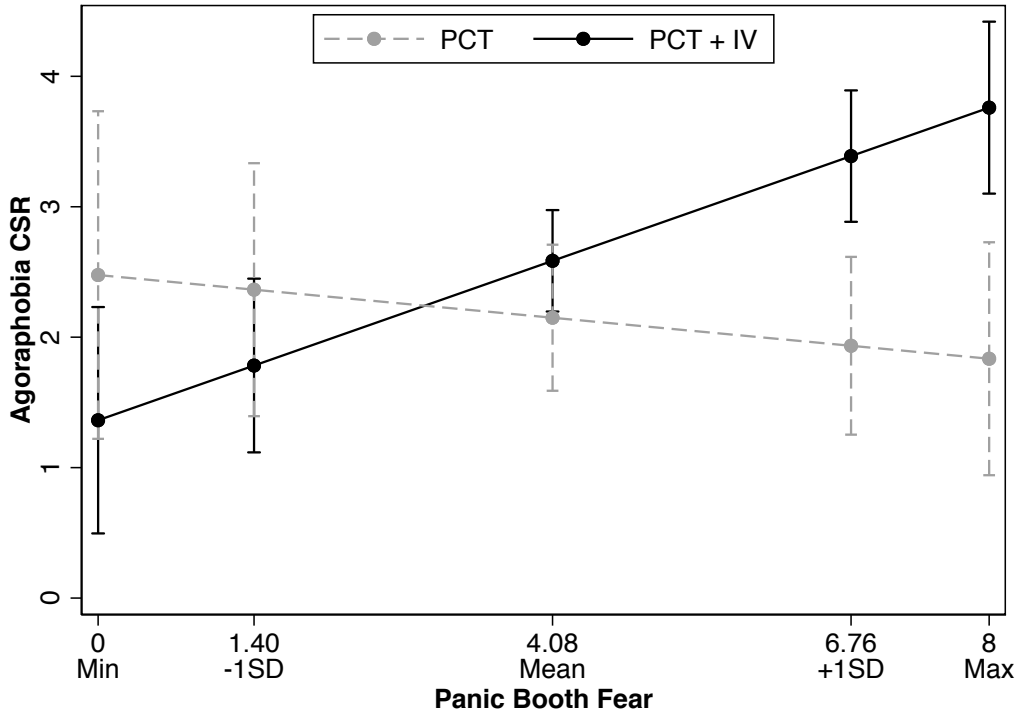
Controlling for panic booth fear, panic booth avoidance significantly interacted with group to moderate agoraphobia CSR, $z = 2.23$, SE = 0.11, $p = .03$, 95% CI [0.03, 0.44], $f^2 = 0.10$ (see Figure 2). Individuals who displayed more panic booth avoidance (i.e., 1 SD below the mean duration) had 1.70 greater CSR after PCT + IV than PCT, $z = 3.01$, SE = 0.50, $p = .003$, 95% CI [0.52, 2.48]. There were no group differences at the mean or at the maximum duration, ps > .05. The slope of the PCT group was not significantly different from zero, $p = .64$, whereas the slope of the PCT + IV group was negative, $z = -3.18$, SE = 0.06, $p = .001$, 95% CI [-0.31, -0.07]. This reveals that individuals with greater panic booth avoidance benefited more from PCT than PCT + IV.

Figure 2. Baseline panic booth avoidance significantly interacted with group to moderate agoraphobia clinical severity rating.



Controlling for panic booth avoidance, panic booth fear significantly interacted with group to moderate agoraphobia CSR, $z = -2.81$, SE = 0.14, $p = .01$, 95% CI [-0.65, -0.11], $f^2 = 0.14$ (see Figure 3). Individuals who reported more panic booth fear (i.e., 1 SD above the mean) had 1.45 greater CSR after PCT + IV than PCT, $z = 3.38$, SE = 0.43, $p = .001$, 95% CI [0.61, 2.30]. There were no group differences at 1 SD below the mean or at the mean, ps > .05. The slope of the PCT group was not significantly different from zero, $p = .50$, whereas the slope of the PCT + IV group was positive, $z = 3.54$, SE = 0.08, $p < .001$, 95% CI [0.13, 0.47]. This reveals that individuals with greater panic booth fear benefitted more from PCT than PCT + IV.

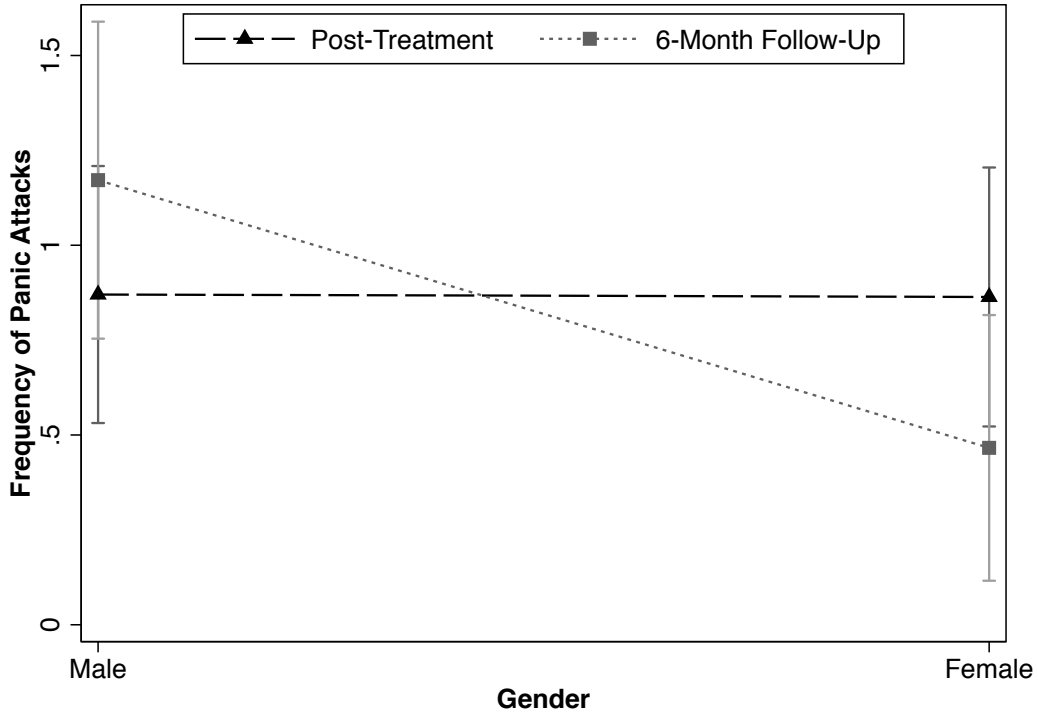
Figure 3. Baseline panic booth fear significantly interacted with group to moderate agoraphobia clinical severity rating.



Demographic and Clinical Characteristics

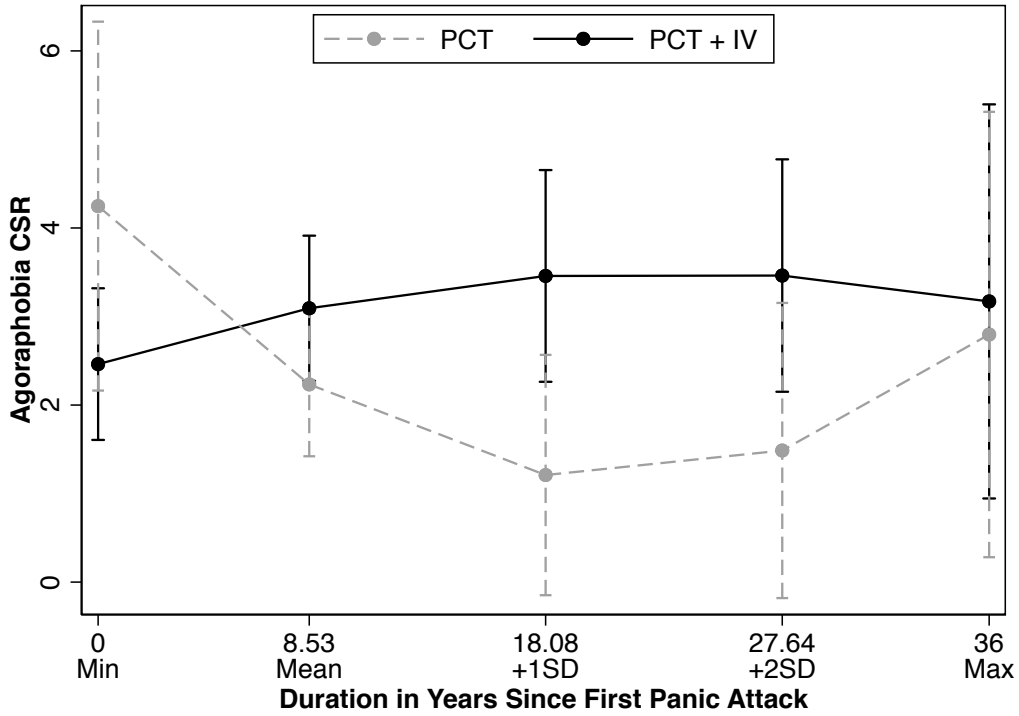
Gender significantly interacted with time to predict the frequency of panic attacks, $F(7, 43) = 2.86$, $p = .02$, $f^2 = 0.10$ (see Figure 4). Adjusting for multiple comparisons, tests of simple effects revealed that at 6-month follow-up, females had 0.71 units less in frequency of panic attacks than males, $t = 2.50$, SE = 0.28, $p = .016$, 95% CI [0.14, 1.28]. There was no significant difference between females and males at post-treatment, $p = .98$. There were also no significant differences within females and within males at each time point, ps > .017.

Figure 4. Gender significantly interacted with group to moderate apprehension of having a panic attack.



The quadratic term of duration since first panic attack significantly interacted with group to moderate apprehension of having a panic attack, $z = 2.06$, $SE = 0.004$, $p = .04$, 95% CI [0.0004, 0.02] (see Figure 5). Adjusting for multiple comparisons, tests of simple effects revealed no significant group differences in apprehension at the mean, minimum, and 1 SD above the mean, ps > .017. We tested the minimum because 1 SD below the mean was outside the possible range. Considering there were no significant differences at these values, we added post hoc tests of simple effects at 2 SD above the mean and maximum score for a total of five tests. Adjusting for multiple comparisons, tests of simple effects revealed no significant group differences in apprehension, ps > .01. Given these results, we did not conduct tests of instantaneous slopes nor did we calculate effect sizes.

Figure 5. Baseline duration since first panic attack significantly interacted with group to moderate agoraphobia clinical severity rating.



Discussion

Primary outcomes from this study revealed that PCT and PCT + IV did not differ significantly in terms of efficacy for panic disorder with or without agoraphobia (Craske et al., 2003). To improve treatment outcomes, we investigated whether certain types of individuals did better overall and whether one treatment was better suited for certain types of individuals than the other. We hypothesized that individuals with more baseline interoceptive avoidance (compared to individuals with less baseline interoceptive avoidance) would benefit more from PCT than PCT + IV because it would target their deficit. Correspondingly, we hypothesized that individuals with more baseline in vivo avoidance (compared to individuals with less baseline in

vivo avoidance) would benefit more from the PCT + IV than PCT. We also tested interoceptive fear, in vivo fear, clinical characteristics, and demographic factors as predictors and moderators.

Baseline interoceptive avoidance did not moderate panic disorder outcomes; however, interoceptive fear moderated apprehension of having a panic attack, such that individuals with greater fear (+2 SD) had less apprehension following PCT than PCT + IV. Contrary to our hypothesis, individuals with high baseline in vivo avoidance and fear (+1 SD) on the panic booth task had higher agoraphobia CSR following PCT + IV compared to PCT. The effect sizes for the aforementioned results ranged from 0.07 to 0.14.[7] Time did not interact with any of the moderators, suggesting that moderation effects continue through 6-month follow-up.

Overall, individuals with higher interoceptive fear, panic booth avoidance, and panic booth fear fared better in PCT than PCT + IV compared to individuals with lower avoidance and fear. One explanation for these results is that highly phobic and avoidant individuals benefit from concentrated doses of exposure to their primary interoceptive concerns. They may be avoiding the panic booth because of fear of their bodily sensations. Indeed, panic disorder was the principal diagnosis for all participants. In line with the notion that a single focused treatment is more beneficial than a treatment that aims to address multiple targets, we previously found that individuals randomized to group CBT for primary diagnoses of panic disorder and agoraphobia did better than individuals randomized to group CBT that also targeted comorbid anxiety disorders (Craske et al., 2007). On the other hand, in a study of 25 individuals with comorbid panic disorder and generalized anxiety disorder (GAD), there were no group differences between individuals who were randomized to receive CBT for their primary diagnosis and those who were randomized to receive CBT for both panic disorder and GAD (Primiano et al., 2014).

[7] Cohen's f^2 of 0.02 and 0.15 are considered small and medium, respectively (Cohen, 1988).

Nevertheless, the study was likely underpowered to detect group differences because of the small sample size.

Another possible explanation for why individuals who have high interoceptive fear, panic booth avoidance, and panic booth fear benefit more from PCT than PCT + IV is that the repetition of treatment in the PCT group provides individuals with an opportunity to develop a greater sense of mastery of treatment material, or greater opportunity to evaluate their progress. Individuals with high panic booth avoidance and fear may do worse in PCT + IV than PCT because eight sessions of in vivo treatment may not be enough to decrease their in vivo avoidance and fear, leaving them to feel as though they have not/ or cannot improve. It is also possible that the repetition of treatment in the PCT group afforded individuals the chance to engage in a larger variety of interoceptive exposures, thereby enhancing extinction learning, compared to those in the PCT + IV group. Unfortunately, we did not include session-by-session measures, nor did we include measures of perceived mastery or progress to test these hypotheses.

Contrary to our hypotheses, interoceptive avoidance did not moderate any outcome measures. One explanation may be that our measure of interoceptive avoidance is limited because it does not capture response to unexplained physiological sensations. Additionally, interoceptive fear only moderated one of three panic disorder outcome measures. Moreover, panic booth avoidance and fear moderated outcomes, whereas diagnostician-rated avoidance and fear did not. This implies that the results are specific to panic booth avoidance rather than to in vivo avoidance of many different places. Alternatively, these results could suggest that diagnosticians may not be particularly accurate at judging levels of participants' behavioral avoidance. The conjecture that panic booth avoidance and diagnostician-rated avoidance are measuring different concepts is somewhat supported by the weak relationship between the two

measures, which we have reported in this paper's Method section under the "in vivo avoidance and fear" heading. Indeed, diagnostician ratings of avoidance are dependent on patient self-report which have been found to be discrepant from actual avoidance in laboratory paradigms (Gamez, Kotov, & Watson, 2010; McNeil, Ries, & Turk, 1995). Similar to our current findings, in a study on moderators of behavioral therapy for social anxiety disorder, we found that behavioral avoidance measured on a public speaking task was a significant moderator of outcomes, but avoidance measured via diagnostician rating was not a significant moderator (Mesri et al., 2017). Lastly, some results may have been non-significant simply because they were underpowered.

As for clinical and demographic characteristics, females had less frequent panic attacks than males by 6-month follow-up. Additionally, the quadratic term of duration since first panic attack was a significant moderator of agoraphobia CSR. Despite a statistically significant model, tests of simple effects revealed only one group difference at 1 SD above the mean.

Overall, our findings provide additional data in the investigation of predictors and moderators of treatment outcomes. Some strengths of the study include using behavioral measures of avoidance rather than reliance on self-report and statistically controlling for avoidance and fear to isolate the effects of each. Our use of group therapy is both a strength and limitation of the study; group CBT is well validated for panic disorder and uses fewer resources per individual than traditional one-on-one therapy, but it limits our generalizability to other formats of CBT (Butler, Chapman, Forman, & Beck, 2006; Schwartze et al., 2017). Inclusion and exclusion criteria for the study further limit generalizability. Other limitations include a small and largely Caucasian sample, low power, and lack of participant details through each phase of the study. The lack of self-report measures is also limiting because the ADIS-IV ratings are fairly restricted and could have limited our ability to detect differences between the

groups. Future studies should consider including longer follow-up intervals, using composite measures, and keeping records of the number and type of exposures that participants conducted in/ between session to better understand these effects. The results are limited, but nonetheless raise the possibility that avoidance and fear can be used as prescriptive factors for treatment matching and personalized care.

DISSERTATION DISCUSSION

This dissertation is a series of three studies that applies theoretical knowledge of avoidance to improve treatment efficacy for individuals with anxiety disorders. Avoidance is posited to maintain anxiety by blocking extinction learning, and exposure therapy is posited to treat anxiety by targeting that avoidance (Lerman, 2003). In study 1, we test whether retraining implicit avoidance can augment extinction learning and decrease avoidance behavior. In studies 2 and 3, we investigate whether avoidant individuals benefit more from one therapy or another.

In study 1, we hypothesized that training implicit approach to feared stimuli would (1) enhance fear extinction and (2) promote approach to feared stimuli, by increasing the salience of the stimuli during extinction learning. Results revealed that training implicit approach or avoidance of feared stimui did not affect fear extinction or future avoidance behavior. Baseline explicit avoidance also did not affect fear extinction, but it did affect future avoidance behavior, such that individuals who reported as highly avoidant at baseline were more likely to avoid feared stimuli at the end of the study compared to individuals who were reported as less avoidant. We did not find an effect of retraining implicit biases in an unambiguous fear conditioning design, but these results could change under difference circumstances (e.g., more power, ambiguous fear conditioning design).

In study 2, we investigated whether individuals with baseline avoidance fare better in one of two behavioral therapies (CBT, ACT) for social anxiety disorder. Both CBT and ACT target avoidance; however, CBT more explicitly targets behavioral avoidance, whereas ACT more specifically targets experiential avoidance. From a deficit correction model, we hypothesized that individuals who are more behaviorally avoidant at baseline would benefit more from CBT than ACT (compared to individuals who are less avoidant) because CBT more systematically targets

that type of avoidance. Behavioral avoidance was measured in two ways (1) in vivo avoidance of a public speaking task and (2) clinician rating of 14 social situations. Results revealed that individuals who were highly avoidant of the baseline public speaking task fared better by 12-month follow-up after CBT than ACT compared to individuals who were less avoidant at baseline. Conversely, clinician-rated social avoidance did not moderate outcome, suggesting that the results are specific to public speaking avoidance versus general social avoidance. Alternatively, the divergent findings may be a result of low power. Despite limitations, this study suggests that baseline avoidance can play a prescriptive role in matching treatments to individuals.

Seeing as avoidance was a significant moderator of treatment outcome in social anxiety disorder, in study 3, we attempt to replicate and expand those findings by investigating avoidance as a treatment moderator for panic disorder. We tested whether individuals with baseline interoceptive and in vivo avoidance benefit more from one of two treatments for panic disorder: (1) CBT with interoceptive exposures or (2) CBT with mixed exposures (i.e., interoceptive and in vivo exposures). From a deficit correction perspective and in line with previous findings (e.g., study 2), we hypothesized that individuals with more interoceptive avoidance would benefit more from CBT with interoceptive exposures than CBT with mixed exposures, compared to individuals with less interoceptive avoidance. Additionally, we hypothesized that individuals with more in vivo avoidance would benefit more from CBT with mixed exposures than CBT with interoceptive exposures, compared to individuals with less in vivo avoidance. Contrary to our hypotheses, individuals who displayed more in vivo avoidance at baseline benefitted more from CBT with interoceptive exposures than CBT with mixed exposures compared to individuals with less in vivo avoidance. Interoceptive avoidance did not

moderate outcome. This suggests that individuals with panic disorder who have high in vivo avoidance benefit more from exposures to their main interoceptive concerns as opposed to exposures to both interoceptive and in vivo avoidance. This study provides additional support for using baseline avoidance for clinical decision-making when treatment planning.

Strengths across all three studies include measuring different types of avoidance (e.g., implicit, explicit, interoceptive, in vivo) using a range of methods (e.g., behavioral, self-report, clinician-rated). In both studies 2 and 3, behavioral measures of avoidance moderated outcome, but clinician-rated avoidance did not. As mentioned before, it is possible that null findings were because of low power or other reasons. Nevertheless, we are interested in whether this effect is replicated in other studies. If so, it may suggest that clinician-rated avoidance is not as useful in treatment prescription than behavioral avoidance. Instead of interviewing patients to rate their level of avoidance, clinicians may want to ask their patients to stand up and engage in a behavioral task. This behavioral measure may be more ecologically valid than clinician interviews, which rely partly on patient report.

Taken together, this dissertation highlights the important role of avoidance as a maintenance factor and potential prescriptive factor in anxiety disorders. Improving our ability to prescribe treatments can enhance treatment response. Moreover, research in this area also helps expand our theoretical understanding of anxiety, avoidance, and behavioral treatments.

Appendix

Brief Clinician Protocol for Assessing Public Speaking Avoidance

"I would like you to give a 3-minute speech while standing up. I will be observing you and may also videotape you in order to evaluate the speech on content and delivery later. I would like you to talk about global warming and/or corporeal punishment. You can talk about one or both of the topics. I will give you 5 minutes to prepare your speech. You can write notes on a piece of paper but you cannot use the paper when you are speaking."

GIVE PATIENT PEN AND NOTEPAD

AFTER 5 MINUTES, ASK PATIENT TO STAND AND GIVE THE SPEECH. TIME THE PATIENT.

After 3 minutes have elapsed say: "Would you be willing to continue speaking? You may continue for any amount of time up to 3 minutes. It's up to you. Would you like to continue speaking?"

Record duration of speech.

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